Statistical identification of predictors for peripheral neuropathy associated with administration of bortezomib, taxanes, oxaliplatin or vincristine using ordered logistic regression analysis

Yuko Kanbayashi[a,b,g], Toyoshi Hosokawa[a,c], Kousuke Okamoto[g], Hideyuki Konishi[d], Eigo Otsuji[e], Toshikazu Yoshikawa[d], Tatsuya Takagi[g,h] and Masafumi Taniwaki[f]

Chemotherapy-induced peripheral neuropathy (CIPN) is a major drug-induced adverse reaction that becomes a dose-limiting toxicity. However, effective strategies for preventing or treating CIPN are lacking. Accordingly, this study aimed to statistically identify predictors for CIPN. Retrospective analysis was carried out for 190 patients who had been treated with bortezomib ($n=28$), taxanes (paclitaxel or docetaxel; $n=58$), oxaliplatin ($n=52$) or vincristine ($n=52$) at our hospital between April 2005 and December 2008. The severity of CIPN was assessed at the time of chemotherapy completion, graded as grade 0–5 in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0. Multivariate ordered logistic regression analysis was used to investigate predictors for CIPN. Predictors for CIPN in patients that were administered bortezomib were no co-administration of dexamethasone [odds ratio (OR), 0.455; confidence interval (CI), 0.208–0.955; $P=0.0376$] and sex (male) (OR, 3.035; CI, 1.356–6.793; $P=0.0069$). For taxanes (paclitaxel or docetaxel), the predictor for CIPN was a large number of chemotherapy cycles (OR, 2.379; CI, 1.035–5.466; $P=0.0412$). For oxaliplatin, the predictors for CIPN were a large number of chemotherapy cycles (OR, 3.089; CI, 1.598–5.972; $P=0.0008$) and no co-administration of non-steroidal anti-inflammatory drugs (OR, 0.393; CI, 0.197–0.785; $P=0.0082$). For vincristine, predictors for CIPN were a large number of chemotherapy cycles (OR, 6.015; CI, 1.880–19.248; $P=0.0025$) and co-administration of an analgesic adjuvant (OR, 3.907; CI, 1.383–11.031; $P=0.0101$). In conclusion, our study indicates that CIPN will be alleviated by the co-administration of dexamethasone with bortezomib and non-steroidal anti-inflammatory drugs with oxaliplatin. *Anti-Cancer Drugs* 21:877–881 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Anti-Cancer Drugs 2010, **21**:877–881

Keywords: bortezomib, chemotherapy, oxaliplatin, peripheral neuropathy, taxanes, vincristine

[a]Department of Pain Treatment & Palliative Care Unit, [b]Hospital Pharmacy, University Hospital, Kyoto Prefectural University of Medicine, [c]Department of Anaesthesiology, [d]Molecular Gastroenterology and Hepatology, [e]Digestive Surgery, [f]Molecular Haematology and Oncology, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kyoto, [g]Departments of Pharmainformatics and Pharmacometrics, Graduate School of Pharmaceutical Sciences and [h]Genome Information Research Center, Research Institute for Microbial Diseases, Osaka University, Suita, Japan

Correspondence to Yuko Kanbayashi, MPh, Department of Hospital Pharmacy, Kyoto Prefectural University of Medicine, Kawaramachi Hirokoji, Kamigyo-ku, Kyoto 602-8566, Japan
Tel: +81 75 251 5865; fax: +81 75 251 5863;
e-mail: ykokanba@koto.kpu-m.ac.jp.

Received 6 June 2010 **Revised form accepted** 30 June 2010

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) accompanies the administration of drugs such as molecularly targeted therapeutic agents (bortezomib), taxanes (paclitaxel, docetaxel), platinum-containing drugs (oxaliplatin) and vinca alkaloids (vincristine), and is a major drug-induced adverse reaction that becomes a dose-limiting toxicity of chemotherapy [1–6]. CIPN has been postulated as an initial stage in the development of neuropathic pain. However, effective strategies for preventing or treating CIPN remain elusive. CIPN manifests in the form of diverse symptoms, and seriously reduces the quality of life (QOL) for the patient.

This study was designed and conducted on the premise that statistical identification of significant predictors for CIPN would contribute to improving the QOL for patients undergoing chemotherapy. This study was carried out after having obtained approval from the Ethics Review Boards of Kyoto Prefectural University of Medicine and Osaka University.

Patients and methods

Study term and patients

This study was carried out as a retrospective analysis of 190 patients who had been treated in the Departments of Haematology and Oncology, Gastroenterology and Hepatology and Digestive Surgery of the University Hospital at Kyoto Prefectural University of Medicine between April 2005 and December 2008. The patients had been administered a molecularly targeted drug (bortezomib, $N=28$), taxane (paclitaxel, $N=14$ or docetaxel, $N=44$), platinum-containing drug (oxaliplatin, $N=52$) or vinca alkaloid (vincristine, $N=52$).

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32833db89d

Statistical analysis

Extraction of variables

Variables were extracted for analysis by regression analysis of factors related to the occurrence of CIPN [2,4–9]. Predictor X included demographic factors, co-morbidity 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 CIPN ($= Y$). Binary scales were used for sex (female = 0; male = 1), age (< 60 years = 0; $\geq$ 60 years = 1), drug administration (no = 0; yes = 1) and miscellaneous (no = 0; yes = 1). The number of chemotherapy cycles was graded according to an ordinal scale (< 6 cycles = 0; 6–10 cycles = 1; > 10 cycles = 2). Response Y was defined as the severity of CIPN assessed at the time of chemotherapy completion, graded as grade 0–5 in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0, in terms of neuropathy and sensory severity. Patients with a history of peripheral neuropathy (PN) were excluded from the participants (absence of the baseline PN).

Statistical–analytical approach

The actual procedure used was a multivariate ordered logistic regression analysis, as CIPN was evaluated by a graded scale, and as multiple factors involved in CIPN must be evaluated simultaneously. Variables were screened by examining for multicollinearity (correlation coefficient $r > 0.7$), which occurs when correlations exist among the variables and results in the use of an inappropriate model. Variables were further screened with the forward selection procedure, after which multivariate logistic regression analysis was performed with the selected variables (JMP Version 8; SAS Institute, Cary, North Carolina, USA). All statistical analyses were performed at the two-sided 0.05 significance level.

Results

Table 1 presents the clinical characteristics of the patients administered bortezomib, taxanes (paclitaxel or docetaxel), oxaliplatin or vincristine, and selected predictors ($= X$) related to the manifestation of CIPN. The analgesic adjuvants that were co-administered consisted of antiepileptic agents (gabapentin, clonazepam, and carbamazepine), tricyclic antidepressants (amitriptyline), mexiletine, vitamin B_{12} and Japanese herbs (Shakuyaku-Kanzo-To and Gosha-Jinki-Gan). The chemotherapeutic regimen comprised, in the case of bortezomib (1.0–1.3 mg/m^2), single use of bortezomib or a combination of bortezomib with dexamethasone or thalidomide. Similarly for the taxanes, the chemotherapeutic regimen consisted of single use of a taxane (paclitaxel; 80–100 mg/m^2 for 6 times in an 8-week or docetaxel; 60–70 mg/m^2 for every 3–4 weeks), or combination of a taxane with tegafur, 5-chloro-2, 4-dihydroxypyridine, and oteracil potassium (TS-1), 5-fluorouracil (5-FU) or cisplatin. For oxaliplatin (85 mg/m^2), the chemotherapeutic regimen consisted of oxaliplatin with 5-FU and leucovorin (FOLFOX-6) in some cases with bevacizumab. For vincristine, the regimens comprised combinations of cyclophosphamide with doxorubicin,

Table 1 Clinical characteristics of patients and factors potentially affecting occurrence of peripheral neuropathy

	Bortezomib (N=28)	Taxanes (N=58)	Oxaliplatin (N=52)	VCR (N=52)
Demographic				
Sex (male), *N* (%)	16 (57.1)	36 (62.1)	32 (61.5)	27 (51.9)
Age, mean (SD)	59.9 (13.9)	65.3 (9.3)	62.2 (12.3)	63.8 (13.0)
Age $\geq$ 60 years, *N* (%)	17 (60.7)	40 (67.0)	32 (61.5)	25 (48.1)
Comorbidity				
DM, *N* (%)	3 (10.7)	5 (8.6)	6 (11.5)	4 (7.7)
Concomitant medication				
Opioid, *N* (%)	5 (17.9)	8 (13.7)	10 (19.2)	8 (15.4)
NSAIDs, *N* (%)	8 (28.6)	21 (36.2)	16 (30.8)	12 (23.1)
NSAIDs (COX-2), *N* (%)	–	10 (17.2)	–	–
Analgesic adjuvant, *N* (%)	17 (60.7)	–	8 (15.4)	10 (19.2)
Concomitant use of cancer drugs				
DEX, *N* (%)	13 (46.4)	–	–	5 (9.6)
Thalidomide, *N* (%)	1 (3.8)	–	–	–
Cisplatin, *N* (%)	–	14 (24.1)	–	–
TS-1, *N* (%)	–	12 (20.7)	–	–
Number of chemotherapy cycles (1), mean (range)	11.1 ± 14.5 (3–75)	6.6 ± 7.7 (1–46)	8.2 ± 6.0 (1–25)	3.8 ± 2.9 (1–18)
Number of chemotherapy cycles (2) (0/1/2)[a]	9/14/5	34/17/7	20/19/13	37/15/0
Type of cancer				
Gastric cancer, *N* (%)		20 (34.5)		
Esophageal cancer, *N* (%)		35 (60.3)		
Cecal cancer, *N* (%)		1 (1.7)		
Cholangiocarcinoma, *N* (%)		1 (1.7)		
Malignant mesothelioma, *N* (%)		1 (1.7)		
Colorectal cancer, *N* (%)			52 (100)	
MM, *N* (%)	28 (100)			5 (9.6)
NHL, *N* (%)				39 (75.0)
Leukemia, *N* (%)				8 (15.4)

COX, cyclooxygenase; DEX, dexamethasone; DM, diabetes mellitus; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; NSAID, non-steroidal anti-inflammatory drug; TS-1, tegafur, 5-chloro-2,4-dihydroxypyridine, and oteracil potassium; VCR, vincristine.

[a]Ordinary scales were <6 cycles=0, 6–10 cycles=1, >10 cycles=2 for number of chemotherapy cycles (2).

vincristine (1.4 mg/m^2, maximum dose, 2.0 mg/body) and prednisone or vincristine (0.4 mg × 4/body) with doxorubicin and dexamethasone, while vincristine (1.4 mg/m^2, maximum dose; 2.0 mg/body) with prednisone, daunorubicin and L-asparaginase in some cases with imatinib was used as an induction therapy for acute lymphoblastic leukemia, and combinations of cytarabine with etoposide, dexamethasone, and vincristine (1 mg/m^2, maximum dose; 2.0 mg/body), and 6-mercaptopurine with vincristine (1 mg/m^2, maximum dose; 2.0 mg/body) were administered as a postinduction regimen.

Table 2 shows data on the severity of CIPN at the time of chemotherapy completion, rated as grade 0–5 in accordance with the Common Terminology Criteria for Adverse Events v3.0. The minimum number of patients necessary to form a category of the response (= *Y*) was four in logistic regression analysis, and each category of *Y* was divided into two or three (Table 3).

Table 2 Results of sensory peripheral neuropathy assessment using CTCAE v3.0

	Number of patients			
CTCAE v3.0	Bortezomib (*n*=28)	Taxanes (*n*=58)	Oxaliplatin (*n*=52)	Vincristine (*n*=52)
0	10	48	26	31
1	5	2	8	3
2	6	4	16	15
3	7	4	2	3
4	0	0	0	0
5	0	0	0	0

CTCAE, Common Terminology Criteria for Adverse Events.

Table 3 Response(*Y*): Categorization of data for sensory peripheral neuropathy

	Number of patients			
Dependent variable (*Y*)	Bortezomib (*n*=28)	Taxanes (*n*=58)	Oxaliplatin (*n*=52)	Vincristine (*n*=52)
0	10	48	26	31
1	5	6	8	
2	6		18	21
3	7	4		

For patients who were administered bortezomib, the predictors identified in this manner for CIPN were no co-administration of dexamethasone [odds ratio (OR), 0.455; confidence interval (CI), 0.208–0.955; $P = 0.0376$] and sex (male) (OR, 3.035; CI, 1.356–6.793; $P = 0.0069$). For taxanes (paclitaxel or docetaxel), the predictor for CIPN was a large number of chemotherapy cycles (OR, 2.379; CI, 1.035–5.466; $P = 0.0412$). For oxaliplatin, the predictors for CIPN were a large number of chemotherapy cycles (OR, 3.089; CI, 1.598–5.972; $P = 0.0008$) and no co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) (OR, 0.393; CI, 0.197–0.785; $P = 0.0082$). For vincristine, the predictors for CIPN were a large number of chemotherapy cycles (OR, 6.015; CI, 1.880–19.248; $P = 0.0025$) and co-administration of an analgesic adjuvant (OR, 3.907; CI, 1.383–11.031; $P = 0.0101$) Accuracy means the ratio of patients whose expected value is equal to observed value (Table 4).

Discussion

Predictors for CIPN were elucidated by statistical analysis. When bortezomib was administered, CIPN showed an increased tendency to develop when the patient was male and dexamethasone was not co-administered. In the case of taxane administration, CIPN showed an increased tendency to develop that was proportional to the number of drug administration cycles. The administration of oxaliplatin tended to show increased incidence of CIPN as the number of drug administration cycles increased and when no NSAIDs were co-administered. Vincristine tended to show an increased incidence of CIPN as the number of drug administration cycles increased, and also even when an analgesic adjuvant was co-administered.

In the case of a complication of diabetes mellitus, the administration of thalidomide reportedly became a predictor for bortezomib-induced PN [7]. Reducing the

Table 4 Results of logistic regression analysis for variables extracted by forward selection

						CI of OR	
Variable	EV	SE	χ^2 value	*P*	OR	Lower 95%	Upper 95%
Table 4-1: Bortezomib (accuracy=14/28)							
DEX	−0.809	0.389	4.32	0.0376*	0.445	0.208	0.955
Sex (male)	1.110	0.411	7.30	0.0069*	3.035	1.356	6.793
Table 4-2: Taxanes (accuracy=49/58)							
Number of chemotherapy cycles (2)	0.867	0.424	4.17	0.0412*	2.379	1.035	5.466
DM	0.690	0.495	1.94	0.1632	1.993	0.756	5.257
Table 4-3: Oxaliplatin (accuracy=34/52)							
Number of chemotherapy cycles (2)	1.128	0.336	11.25	0.0008*	3.089	1.598	5.972
NSAIDs	−0.934	0.353	7.00	0.0082*	0.393	0.197	0.785
Table 4-4: Vincristine (accuracy=42/52)							
Age	0.795	0.458	3.01	0.0828	2.215	0.902	5.438
Number of chemotherapy cycles (2)	1.794	0.593	9.14	0.0025*	6.015	1.880	19.248
Analgesic adjuvant	1.363	0.530	6.62	0.0101*	3.907	1.383	11.031
NSAIDs	0.842	0.460	3.35	0.0670	2.320	0.943	5.711

CI, confidence interval; DEX, dexamethasone; DM, diabetes mellitus; EV, estimated value; NSAIDs, non-steroidal anti-inflammatory drugs; OR, odds ratio; SE, standard error.
*$P<0.05$.

dosage of bortezomib and/or changing the treatment schedule are also reportedly effective in alleviating bortezomib-induced PN [8]. This study did not find the number of chemotherapy administration cycles or diabetes mellitus to be predictors for bortezomib-induced PN. In addition, the use of thalidomide is not covered by the health insurance system in Japan; therefore few patients received co-administration and we did not include this agent in our analysis (thalidomide was co-administered to only one of the 28 patients treated with bortezomib). Our finding showed that co-administration of dexamethasone was able to alleviate bortezomib-induced PN. A recent report found that the immune system is involved in bortezomib-induced PN [9], and the administration of a steroid may thus contribute to mitigating the involvement of the immune system. In addition, we found that bortezomib-induced PN tended to manifest in male patients. No reports of sex differences in CIPN have been described. Although Mileshkin *et al.* [10] studied the occurrence of PN in patients treated with thalidomide, they also found no sex differences. As for cancer pain, an earlier study clarified that pain was significantly exacerbated when the patient was male [11]. This issue of sex-related bortezomib-induced PN warrants further investigation.

PN because of the administration of taxanes (paclitaxel, docetaxel) showed a tendency to occur as the number of cycles of chemotherapy increased. This result supports earlier reports that PN is a dose-limiting factor in taxane therapy [12–14].

Our analysis showed that that the co-administration of NSAIDs was effective in alleviating sensory PN because of oxaliplatin. Several groups have reported cyclooxygenase (COX) 2-dependent prostaglandin E2 as a causative factor in PN [15–18]. Moreover, there have been reports that COX-2 is involved in diabetic PN, although that pathology is a separate entity to CIPN [19,20]. Further investigation will be needed to elucidate the prophylactic efficacy of COX2-specific NSAIDs in relation to CIPN.

CIPN because of vincristine administration showed a tendency to occur as the number of chemotherapy cycles increased. This result supports earlier reports that PN because of vincristine was a dose-limiting factor for this therapy [21–23]. Moreover, analgesic adjuvants, used to relieve the symptoms derived from PN itself during chemotherapy, did not show adequate prophylactic efficacy. This finding supports earlier observations that no effective analgesic adjuvants are currently available for CIPN [1–6].

Various analgesic adjuvants, including antidepressants and antiepileptics, have been tried as therapeutic agents for CIPN, but no such drugs have shown clear efficacy. These results were in agreement in that regard, with CIPN occurring even with co-administration of analgesic adjuvants. In addition, although an opioid was reportedly effective in relieving PN [24,25], this study did not identify the lack of co-administration of opioids as a predictor for CIPN. Further research is warranted with regard to the potential prophylactic effects of agents such as steroids, NSAIDs (particularly COX2-specific NSAIDs), analgesic adjuvants and opioids in relation to CIPN.

In conclusion, we used a statistical approach to identify predictors for CIPN. Our study indicates that CIPN will be alleviated by the co-administration of dexamethasone with bortezomib and NSAIDs with oxaliplatin. Our study has limitations in terms of the retrospective nature of the investigation and the relatively small number of patients analyzed, but the statistical identification of predictors for CIPN should contribute to the establishment of evidence-based medicine in the prophylaxis of CIPN and improving QOL for patients undergoing chemotherapy.

Disclosures: none.

References

1 Kannarkat G, Lasher EE, Schiff D. Neurologic complications of chemotherapy agents. *Curr Opin Neurol* 2007; **20**:719–725.
2 Windebank AJ, Grisold W. Chemotherapy-induced neuropathy. *J Peripher Nerv Syst* 2008; **13**:27–46.
3 Wolf S, Barton D, Kottschade L, Grothey A, Loprinzi C. Chemotherapy-induced peripheral neuropathy: prevention and treatment strategies. *Eur J Cancer* 2008; **44**:1507–1515.
4 Park SB, Krishnan AV, Lin CS, Goldstein D, Friedlander M, Kiernan MC. Mechanisms underlying chemotherapy-induced neurotoxicity and the potential for neuroprotective strategies. *Curr Med Chem* 2008; **15**:3081–3094.
5 Ocean AJ, Vahdat LT. Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. *Support Care Cancer* 2004; **12**:619–625.
6 Walker M, Ni O. Neuroprotection during chemotherapy: a systematic review. *Am J Clin Oncol* 2007; **30**:82–92.
7 Badros A, Goloubeva O, Dalal JS, Can I, Thompson J, Rapoport AP, *et al.* Neurotoxicity of bortezomib therapy in multiple myeloma: a single-center experience and review of the literature. *Cancer* 2007; **110**:1042–1049.
8 Argyriou AA, Iconomou G, Kalofonos HP. Bortezomib-induced peripheral neuropathy in multiple myeloma: a comprehensive review of the literature. *Blood* 2008; **112**:1593–1599.
9 Ravaglia S, Corso A, Piccolo G, Lozza A, Alfonsi E, Mangiacavalli S, *et al.* Immune-mediated neuropathies in myeloma patients treated with bortezomib. *Clin Neurophysiol* 2008; **119**:2507–2512.
10 Mileshkin L, Stark R, Day B, Seymour JF, Zeldis JB, Prince HM. Development of neuropathy in patients with myeloma treated with thalidomide: patterns of occurrence and the role of electrophysiologic monitoring. *J Clin Oncol* 2006; **24**:4507–4514.
11 Kanbayashi Y, Okamoto K, Ogaru T, Hosokawa T, Takagi T. Statistical validation of the relationships of cancer pain relief with various factors using ordered logistic regression analysis. *Clin J Pain* 2009; **25**:65–72.
12 Argyriou AA, Koltzenburg M, Polychronopoulos P, Papapetropoulos S, Kalofonos HP. Peripheral nerve damage associated with administration of taxanes in patients with cancer. *Crit Rev Oncol Hematol* 2008; **66**:218–228.
13 Hagiwara H, Sunada Y. Mechanism of taxane neurotoxicity. *Breast Cancer* 2004; **11**:82–85.
14 Makino H. Treatment and care of neurotoxicity from taxane anticancer agents. *Breast Cancer* 2004;**11**:100–104.
15 Ma W, Quirion R. Does COX2-dependent PGE2 play a role in neuropathic pain? *Neurosci Lett* 2008; **437**:165–169.
16 Suyama H, Kawamoto M, Gaus S, Yuge O. Effect of etodolac, a COX-2 inhibitor, on neuropathic pain in a rat model. *Brain Res* 2004; **1010**:144–150.
17 Broom DC, Samad TA, Kohno T, Tegeder I, Geisslinger G, Woolf CJ. Cyclooxygenase 2 expression in the spared nerve injury model of neuropathic pain. *Neuroscience* 2004; **124**:891–900.

18 Vo T, Rice AS, Dworkin RH. Non-steroidal anti-inflammatory drugs for neuropathic pain: how do we explain continued widespread use? *Pain* 2009; **143**:169–171.
19 Kellogg AP, Cheng HT, Pop-Busui R. Cyclooxygenase-2 pathway as a potential therapeutic target in diabetic peripheral neuropathy. *Curr Drug Targets* 2008; **9**:68–76.
20 Kellogg AP, Wiggin TD, Larkin DD, Hayes JM, Stevens MJ, Pop-Busui R. Protective effects of cyclooxygenase-2 gene inactivation against peripheral nerve dysfunction and intraepidermal nerve fiber loss in experimental diabetes. *Diabetes* 2007; **56**:2997–3005.
21 Ja'afer FM, Hamdan FB, Mohammed FH. Vincristine-induced neuropathy in rat: electrophysiological and histological study. *Exp Brain Res* 2006; **173**:334–345.
22 Verstappen CC, Koeppen S, Heimans JJ, Huijgens PC, Scheulen ME, Strumberg D, *et al.* Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. *Neurology* 2005; **64**:1076–1077.
23 Weintraub M, Adde MA, Venzon DJ, Shad AT, Horak ID, Neely JE, *et al.* Severe atypical neuropathy associated with administration of hematopoietic colony-stimulating factors and vincristine. *J Clin Oncol* 1996; **14**:935–940.
24 Gatti A, Sabato AF, Occhioni R, Colini Baldeschi G, Reale C. Controlled-release oxycodone and pregabalin in the treatment of neuropathic pain: results of a multicenter Italian study. *Eur Neurol* 2009; **61**:129–137.
25 Watson CP, Moulin D, Watt-Watson J, Gordon A, Eisenhoffer J. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. *Pain* 2003; **105**:71–78.