Predictors for Development of Oxaliplatin-induced Peripheral Neuropathy in Cancer Patients as Determined by Ordered Logistic Regression Analysis

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Abstract

Purpose This retrospective study aimed to identify predictors for the development of oxaliplatin-induced peripheral neuropathy (OXAIPN).

Methods Between January 2017 and March 2021, a total 322 cancer patients at our hospital who were receiving oxaliplatin were enrolled. For the regression analysis of factors associated with oxaliplatin-induced peripheral neuropathy, variables were extracted manually from medical charts. The level of OXAIPN was evaluated using the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 5). Multivariate ordered logistic regression analysis was performed to identify predictors for the development of OXAIPN. Optimal cut-off thresholds were determined using receiver operating characteristic (ROC) analysis. Values of P <0.05 (2-tailed) were considered significant.

Results Significant factors identified included body mass index (BMI) (odds ratio [OR] = 1.06, 95% confidence interval [CI] = 1.00–1.12; P = 0.046), number of cycles (OR = 1.09, 95%CI = 1.05–1.14; P <0.0001), S-1 plus oxaliplatin (SOX) regimen (OR = 0.54, 95%CI = 0.32–0.92; P = 0.023), concomitant use of proton pump inhibitors (PPIs) (OR = 1.64, 95%CI = 1.05–2.58; P = 0.031) and concomitant use of analgesic adjuvant (OR = 3.30, 95%CI = 1.09–9.97; P = 0.035).

Conclusion BMI, number of cycles, SOX regimen, concomitant use of PPIs and concomitant use of analgesic drugs were identified as significant predictors for the development of OXAIPN.

Introduction

Oxaliplatin is a platinum-derivative chemotherapeutic agent used for chemotherapy in patients with colorectal, pancreatic, and gastric cancer [1–3]. Oxaliplatin causes acute cold-induced neurotoxicity and chronic cumulative neuropathy, which can require dose modification and impacts quality of life (QOL) [4–6]. Early identification of the neurotoxicity and changes in dosage or dosing schedule could prevent the development of chronic symptoms, which, once established, may take many months or years to resolve, or may even persist throughout life with substantial detrimental effects on QOL. However, to date, preventative and therapeutic strategies have not proven effective and identification of patients at risk is therefore important to maximize therapeutic efficacy while minimizing neurotoxicity. In addition, individual differences are seen in the severity of oxaliplatin-induced peripheral neuropathy (OXAIPN). This retrospective study was therefore undertaken to identify predictors associated with the development of OXAIPN to help guide future strategies toward improving safety, efficacy, and QOL among cancer patients treated with oxaliplatin.

Patients And Methods

Study Period and Participants

This study retrospectively analysed 322 cancer patients who received oxaliplatin at our hospital between January 2017 and March 2021. The Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine approved this study (approval no. ERB-C-867-3). 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 Declaration of Helsinki and its later amendments. No prospective studies with human participants or animals were performed by any of the authors for this article. Given the retrospective nature of this work, the need to obtain 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.

Extraction of Variables

For the regression analysis of factors associated with OXAIPN, variables were extracted manually from medical charts. Evaluated variables included factors that could potentially impact the development of OXAIPN: demographic data (sex, age, height, weight, body surface area and BMI), type of cancer, number of cycles, concomitant medications (PPIs, RAS inhibitors, analgesic adjuvant), chemotherapy regimen, presence of comorbidities (diabetes mellitus), and laboratory test values. Creatinine clearance was estimated using the Cockcroft and Gault equation based on serum creatinine, sex, age, and weight. Clinical information was extracted before administration of the first dose of oxaliplatin. Concomitant medication was defined as administration of another drug for ≥2 weeks at the time of evaluation. The level of OXAIPN was evaluated using the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI-CTCAE; version 5). The degree of OXAIPN was evaluated at the time of final oxaliplatin administration.

Statistical Analysis

Independent variables were analysed for multicollinearity (correlation coefficient $|r| \geq 0.7$), since correlations among variables can lead to unreliable and unstable results of regression analyses. Independent variables were extracted based on the strength of the correlation with the level of OXAIPN (dependent variable) or clinical significance. First, univariate ordered logistic regression analyses between outcomes and each potential independent variable were performed. Subsequently, a multivariate ordered logistic regression model was constructed by employing the forward-backward stepwise selection procedure with the resulting candidate variables. The model used a variable entry criterion of 0.15 and a variable retention criterion of 0.1. Ordered logistic regression analysis was employed, because the level of OXAIPN was evaluated by a graded scale and multiple factors really associated as predictors for the development of OXAIPN had to be analysed concurrently. Optimal cut-off thresholds were determined using ROC curve analysis.

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

Results

All 322 patients who received oxaliplatin were enrolled in this study. Table 1 presents the clinical characteristics of the 322 enrolled patients, the potential variables related to the development of OXAIPN, and the results of univariate analyses. Stepwise selection identified the following candidate variables: male sex, body mass index (BMI), number of cycles, chemotherapy regimen as a combination of 5-fluorouracil, oxaliplatin, irinotecan and leucovorin (FOLFIRINOX) or S-1 plus oxaliplatin (SOX), use of renin-angiotensin system (RAS) inhibitors, use of proton pump inhibitors (PPIs), and use of analgesic adjuvants (mirogabalin, pregabalin, or duloxetine). S-1 is an orally available chemotherapeutic agent comprising tegafur (a prodrug of fluorouracil [5-FU]), gimeracil (preventing dihydropyrimidine dehydrogenase-mediated degradation of 5-FU), and oteracil (reducing the toxic effects of 5-FU). Multivariate ordered logistic regression analysis was performed using these variables. Significant factors identified included BMI (odds ratio [OR] = 1.06, 95% confidence interval [CI] = 1.00–1.12; $P = 0.046$), number of cycles (OR = 1.09, 95%CI = 1.05–1.14; $P < 0.0001$), SOX regimen (OR = 0.54, 95%CI = 0.32–0.92; $P = 0.023$), concomitant use of PPI (OR = 1.64, 95%CI = 1.05–2.58; $P = 0.031$) and concomitant use of analgesic adjuvant (OR = 3.30, 95%CI = 1.09–9.97; $P = 0.035$) (Table 2). Receiver operating characteristic (ROC) analysis revealed that OXAIPN (grade 2 or higher) was more likely to occur with BMI $\geq$20.5 kg/m^2, with 63.3% sensitivity and 47.8% specificity (area under the curve [AUC] = 0.54), and number of cycles $\geq$8 cycles, with 66.3% sensitivity and 56.5% specificity (AUC = 0.65).

Table 1
Patient characteristics, extracted variables, and results of univariate analyses (n = 322)

	Grade 0 (n = 64)	Grade 1 (n = 165)	Grade 2 (n = 69)	Grade 3 (n = 23)	*P* value	Odds ratio (95%CI)
Demographic data						
Male, n (%)	50 (76.9)	105 (63.6)	38 (55.1)	14 (60.9)	0.015*	0.58 (0.38-0.90)
Age (y), median (range)	69 (46-88)	70 (32-90)	68 (39-86)	67 (27-83)	0.279	0.99 (0.97-1.01)
Height (cm), median (range)	164.8 (147.5-189.2)	163.5 (145-184.8)	165.1 (142-177.6)	164.5 (145-176)	0.097	0.98 (0.96-1.00)
Weight (kg), median (range)	54.8 (28.4-94)	55.3 (31.1-89)	55.6 (31.2-103)	59 (39.3-80)	0.598	1.00 (0.99-1.10)
BMI (kg/m^2), median (range)	20.6 (12.2-31.2)	20.8 (12.7-30.7)	20.8 (13.2-33.7)	21.9 (16.1-28.4)	0.117	1.04 (0.99-1.10)
BSA (m^2), median (range)	1.59 (1.14-2.08)	1.59 (1.16-2.09)	1.59 (1.13-2.20)	1.63 (1.33-1.90)	0.877	0.92 (0.30-2.79)
Cancer type						
Gastric, n (%)	28 (43.1)	54 (32.7)	18 (26.1)	6 (26.1)	0.032*	0.62 (0.40-0.96)

CI, confidence interval; BMI, body mass index; BSA, body surface area; FOLFOX, chemotherapy regimen consisting of fluorouracil plus oxaliplatin; SOX, chemotherapy regimen consisting of tegafur gimeracil oteracil potassium capsule (S-1) plus oxaliplatin; XELOX, chemotherapy regimen consisting of capecitabine plus oxaliplatin; FOLFIRINOX, chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin; RAS, renin-angiotensin system; NSAIDs, non-steroidal anti-inflammatory drugs.

*P <0.05

	Grade 0 (n = 64)	Grade 1 (n = 165)	Grade 2 (n = 69)	Grade 3 (n = 23)	*P* value	Odds ratio (95%CI)
Pancreas, n (%)	5 (7.7)	18 (10.9)	5 (7.2)	2 (8.7)	0.899	0.96 (0.47-1.94)
Colorectal, n (%)	32 (49.2)	89 (53.9)	45 (65.2)	14 (60.9)	0.049*	1.52 (1.001-2.31)
Comorbidity						
Diabetes mellitus, n (%)	12 (18.5)	24 (14.5)	8 (11.6)	8 (34.8)	0.763	1.09 (0.62-1.90)
Laboratory test value before administration						
Serum creatinine, mg/dL, median (range)	0.77 (0.35-1.2)	0.73 (0.36-1.92)	0.64 (0.41-1.77)	0.71 (0.36-1.27)	0.446	0.69 (0.26-1.80)
Creatinine clearance, mL/min, median (range)	74.9 (28.2-127.4)	70.1 (34.1-204.7)	71.4 (25-168.1)	82.6 (37.4-119.9)	0.178	1.01 (0.998-1.013)
Number of cycles	5 (1-32)	8 (1-34)	9 (2-31)	8 (1-17)	<.0001*	1.10 (1.05-1.14)
Regimen						
FOLFOX	8 (12.3)	25 (15.2)	20 (29.0)	5 (21.7)	0.014*	1.96 (1.15-3.34)

CI, confidence interval; BMI, body mass index; BSA, body surface area; FOLFOX, chemotherapy regimen consisting of fluorouracil plus oxaliplatin; SOX, chemotherapy regimen consisting of tegafur gimeracil oteracil potassium capsule (S-1) plus oxaliplatin; XELOX, chemotherapy regimen consisting of capecitabine plus oxaliplatin; FOLFIRINOX, chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin; RAS, renin-angiotensin system; NSAIDs, non-steroidal anti-inflammatory drugs.

*P<0.05

	Grade 0 (n = 64)	Grade 1 (n = 165)	Grade 2 (n = 69)	Grade 3 (n = 23)	*P* value	Odds ratio (95%CI)
SOX	27 (41.5)	45 (27.3)	11 (15.9)	5 (21.7)	0.001*	0.46 (0.28-0.73)
XELOX	22 (33.8)	70 (42.4)	30 (43.5)	7 (30.4)	0.624	1.11 (0.73-1.69)
FOLFIRINOX	4 (6.2)	18 (10.9)	6 (8.7)	2 (8.7)	0.729	1.13 (0.56-2.30)
History of treatment with anticancer drugs						
Cisplatin	0	5 (3.0)	3 (8.7)	0	0.390	1.77 (0.48-6.52)
Taxane	1 (1.5)	8 (4.8)	3 (4.3)	2 (8.7)	0.245	1.81 (0.67-4.89)
Oxaliplatin	0	2 (1.2)	3 (4.3)	0	0.206	2.86 (0.56-14.52)
Concomitant medication						
RAS inhibitors	12 (18.4)	19 (11.5)	7 (10.1)	3 (13.0)	0.202	0.67 (0.36-1.24)
Proton pump inhibitor	28 (43.1)	82 (49.7)	32 (46.4)	13 (56.5)	0.473	1.16 (0.77-1.75)

CI, confidence interval; BMI, body mass index; BSA, body surface area; FOLFOX, chemotherapy regimen consisting of fluorouracil plus oxaliplatin; SOX, chemotherapy regimen consisting of tegafur gimeracil oteracil potassium capsule (S-1) plus oxaliplatin; XELOX, chemotherapy regimen consisting of capecitabine plus oxaliplatin; FOLFIRINOX, chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin; RAS, renin-angiotensin system; NSAIDs, non-steroidal anti-inflammatory drugs.

*P<0.05

	Grade 0 (n = 64)	Grade 1 (n = 165)	Grade 2 (n = 69)	Grade 3 (n = 23)	*P* value	Odds ratio (95%CI)
Analgesic adjuvant	2 (3.1)	3 (1.8)	3 (4.3)	4 (17.4)	0.009*	4.19 (1.44-12.19)
Duloxetine	1 (1.5)	2 (1.2)	1 (1.4)	4 (17.4)	0.002*	8.11 (2.17-30.27)
Gabapentinoids *(Pregabalin or mirogabalin)*	1 (1.5)	2 (1.2)	2 (2.9)	0	0.798	1.24 (0.24-6.50)
NSAIDs	4 (6.2)	17 (10.3)	8 (11.6)	1 (4.3)	0.623	1.19 (0.59-2.42)
Opioids	8	15	14	1 (4.3)	0.455	1.27 (0.67-2.40)

CI, confidence interval; BMI, body mass index; BSA, body surface area; FOLFOX, chemotherapy regimen consisting of fluorouracil plus oxaliplatin; SOX, chemotherapy regimen consisting of tegafur gimeracil oteracil potassium capsule (S-1) plus oxaliplatin; XELOX, chemotherapy regimen consisting of capecitabine plus oxaliplatin; FOLFIRINOX, chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin; RAS, renin-angiotensin system; NSAIDs, non-steroidal anti-inflammatory drugs.

*P <0.05

Table 2
Results of multivariate ordered logistic regression analysis for variables extracted by forward selection (n = 322)

Variable	*P* value	Odds ratio	95%CI	
			Lower 95%	Upper 95%
Male	0.139	0.71	0.45	1.12
BMI	0.046*	1.06	1.00	1.12
Number of cycles	<.0001*	1.09	1.05	1.14
SOX	0.023*	0.54	0.32	0.92
FOLFIRINOX	0.179	0.59	0.27	1.28
RAS inhibitors	0.239	0.68	0.35	1.30
Proton pump inhibitors	0.031*	1.64	1.05	2.58
Analgesic adjuvant	0.035*	3.30	1.09	9.97
CI, confidence interval; BMI, body mass index; SOX, chemotherapy regimen consisting of tegafur gimeracil oteracil potassium capsule (S-1) plus oxaliplatin; FOLFIRINOX, chemotherapy regimen consisting of oxaliplatin, irinotecan, fluorouracil, and leucovorin; RAS, renin-angiotensin system.				
*P<0.05				

Discussion

The multivariate ordered logistic regression analysis performed in this study showed that significant predictors for the development of OXAIPN included use of BMI, number of cycles, SOX regimen, concomitant use of PPI and concomitant use of an analgesic adjuvant. Although RAS inhibitor was not extracted as a significant variable in multivariate analysis, the combined use of RAS inhibitors tended to reduce OXAIPN.

In this study, BMI was extracted as a significant predictor for the development of OXAIPN. Obesity has been reported as a risk factor for chemotherapy-induced peripheral neuropathy (CIPN) [7–10]. The results of this study were also consistent with findings from previous studies. When the body fat content is high, anticancer drugs reportedly accumulate in adipose tissue and excretion is thus delayed [11]. This may be one reason why OXAIPN is more likely to occur in obese patients. On the other hand, there are many reports contrary to our result of this study that the effect of anticancer drugs is diminished in obese patients [12]. Further verification is needed in this issue.

The ROC curve analysis revealed a BMI cut-off of 20.5 kg/m^2 for the group likely to develop OXAIPN (grade 2 or higher). World Health Organization have defined obesity or overweight patients as individuals with BMI ≥25 kg/m^2 [13]. However, in this study, CIPN was more likely to occur with BMI ≥20.5 kg/m^2.

This may be due to the difference in physique between Japanese and Westerners. In particular, CIPN in the lower limbs may be partly due to the weight load caused by obesity. Clinicians should pay close attention to the onset of OXAIPN among patients with BMI ≥20.5 kg/m^2, not necessarily the obese population.

The results also showed that OXAIPN was more likely to develop as the number of administration cycles increased. ROC analysis revealed that OXAIPN (grade 2 or higher) was more likely to occur with ≥8 cycles. Regarding the number of doses, OXAIPN reportedly tends to become chronic depending on the total dose [5, 14–17]. Beijers et al. demonstrated that a higher cumulative dose is associated with the development of long-term OXAIPN [15]. Careful attention should be paid to the cumulative dose of oxaliplatin, particularly administration of ≥8 cycles.

Among the chemotherapy regimens, SOX therapy has resulted in a lower risk of developing OXAIPN. SOX therapy is administered every 3 weeks, while FOLFOX and FOLFIRINOX are administered every 2 weeks. The concept of the stop-and-go strategy (strategy of intermittent oxaliplatin treatment) was proposed in the OPTIMOX trial to avoid aggravation of OXAIPN [18]. Our results suggested the severity of OXAIPN can be prevented by increasing the dosing interval. Our results are consistent with the results of OPTIMOX trial that OXAIPN can be avoided using the stop-and-go strategy.

Previous studies have reported PPI as a risk factor for peripheral neuropathy [19–21]. Makunts et al. found a significant increase in a wide variety of peripheral neurological and neuropathic adverse events due to PPI [19]. They reported that an increased gastric pH level correlated with decreased levels of vitamin B12. In turn, B12 deficiency has been associated with reversible peripheral neuropathy [21]. Clinicians should thus be careful in prescribing PPIs when performing chemotherapy with oxaliplatin.

Although analgesic adjuvants tend to be used in combination therapy, the result was that OXAIPN developed even with analgesic adjuvants.

The analgesic adjuvants used to relieve the symptoms of OXAIPN during chemotherapy did not show adequate therapeutic efficacy. This finding supports earlier observations that effective analgesic adjuvants are currently unavailable for CIPN [16, 22, 23].

Although not significant, concomitant use of RAS inhibitors was suggested to prevent OXAIPN [24]. Previous research has reported RAS inhibitors could prevent OXAIPN. Further research is needed on this point.

Several limitations to the current study need to be considered. First, the retrospective nature of the study may have decreased the validity of the data obtained. Second, since this study was performed at a single institute, prospective multicentre studies are needed to confirm the results.

In conclusion, BMI, number of cycles, SOX regimen, concomitant use of PPI and concomitant use of analgesic adjuvant were identified as significant predictors for the development of OXAIPN. However, our

findings need to be confirmed in further studies. Nevertheless, these results may assist in developing strategies to improve the safety, efficacy, and QOL among patients receiving oxaliplatin.

Declarations

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Code availability Not applicable

Ethics approval The Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine approved this study (approval no. ERB-C-867-3). 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 Declaration of Helsinki and its later amendments.

Consent to participate No prospective studies with human participants or animals were performed by any of the authors for this article. Given the retrospective nature of this work, the need to obtain 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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Conflicts of interest All authors declare no conflict of interests concerning this work.

Informed consent No prospective studies with human participants or animals were performed by any of the authors for this article. Given the retrospective nature of this work, the need to obtain 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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