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Chlorine Level as a Predictive Factor for Oxaliplatin-induced Peripheral Neuropathy

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Peripheral neuropathy is a major adverse event associated with oxaliplatin-based chemotherapy and is a major dose-limiting adverse event in clinical practice. However, some patients treated with oxaliplatin may show no or minimal peripheral neuropathy. These differences are still poorly understood. This study was carried out as a retrospective analysis of 77 patient's data that had been treated with oxaliplatin-based regimens at the South Dhaka Medical Center between January 2005 and June 2010. Among them 51 patients data were selected and factor analysis was performed. The serum Chlorine (Cl) level at baseline was significantly higher in patients with a high frequency of peripheral neuropathy (106; range 104-107 vs. 104; range 101-104 mEq L^{-1}, p = 0.02). Principal component analysis showed the variables Cl, body mass index, status of liver metastasis and status of lymph node metastasis were related to the incidence of peripheral neuropathy. Discriminant analysis showed the model had predicted 72.5% of peripheral neuropathy. An understanding of the patient's characteristics could be useful for preventing or predicting oxaliplatin-induced peripheral neuropathy.

Key words: Peripheral neuropathy, oxaliplatin, serum chlorine, predicting factors, FOLFIRI, FOLFOX

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INTRODUCTION

Treatments for colorectal cancer include surgery, chemotherapy, radiation or a combination. Chemotherapy with combination of folic acid, 5-FU and oxaliplatin (FOLFOX) or with folic acid, 5-FU and irinotecan (FOLFIRI) resulted prolonged survival. The efficacy against colorectal cancer has been enhanced by the development of molecular-targeted drugs such as bevacizumab, cetuximab and panitumumab (Tournigand *et al*., 2004; De Gramont *et al*., 2000; Goldberg *et al*., 2004; Saltz *et al*., 2008; Cassidy *et al*., 2008).

Oxaliplatin (Kidani *et al*., 1980), a third-generation platinum agent, is a key drug in the chemotherapy treatment of colorectal cancer. Many clinical trials with FOLFOX and XELOX (in combination with capecitabine and oxaliplatin) regimens have been shown to be useful. The National Comprehensive Cancer Network (NCCN) guidelines currently recommend FOLFOX and XELOX± bevacizumab regimens as first-line therapy for colorectal cancer (Ducreux *et al*., 2011).

According to the Food and Drug Administration (FDA) report and numerous clinical trials (Tournigand *et al*., 2004; De Gramont *et al*., 2000; Goldberg *et al*., 2004; Saltz *et al*., 2008; Cassidy *et al*., 2008; Ibrahim *et al*., 2004), however, oxaliplatin frequently induces characteristic patterns of peripheral neurotoxicity in the form of two distinct types (Gamelin *et al*., 2006). The transient acute and cold-induced peripheral neuropathy experienced during administration or immediately after the administration of oxaliplatin is always reversible without persistent impairment of sensory nerve function and this effect does not require the discontinuation of chemotherapy. However, when treatment is continued, the extent of the symptoms can increase and their duration can be prolonged to the extent of becoming permanent. Chronic peripheral neuropathy, which is characterized by the loss of sensory and motor dysfunction after long-term treatment with oxaliplatin, is a major dose-limiting symptom (Wilson *et al*., 2002). Although, various neuromodulatory agents such as calcium-magnesium infusions (Gamelin *et al*., 2004; Hochster *et al*., 2007), α-lipoic acid (Gedlicka *et al*., 2002), venlafaxine (Durand *et al*., 2003, 2011), amifostine (Penz *et al*., 2001), glutathione (Cascinu *et al*., 2002), glutamine (Wang *et al*., 2007), carbamazepine (Von Delius *et al*., 2007), gabapentin (Mitchell *et al*., 2006) and pregabalin have been proposed to prevent or treat oxaliplatin-induced peripheral neuropathy. However the effectiveness of these agents is still obscure (Saif and Hashmi, 2008; Saif *et al*., 2010). OPTIMOX study shows the stop-and-go concept with intermittent administration of oxaliplatin to reverse oxaliplatin-induced neurotoxicity is possible (Tournigand *et al*., 2006). The predictability of oxaliplatin-induced peripheral neuropathy should not only allow medical staff to manage this adverse event but also improve the quality of life. Therefore, this study investigated the predictive factors associated with the incidence and frequency of oxaliplatin-induced peripheral neuropathy.

MATERIALS AND METHODS

Patients: This study was carried out as a retrospective analysis of 77 patients who had been treated with FOLFOX4 (De Gramont *et al*., 1988), mFOLFOX6 (Shimizu *et al*., 2007) or mFOLFOX6 plus bevacizumab at the South Dhaka Medical Center between January 2005 and June 2010. The clinical characteristics at baseline and any adverse events were determined from the electronic medical records or paper medical records. Adverse events (peripheral neuropathy, stomatitis, fatigue, anorexia, nausea, vomiting, diarrhea and constipation) were evaluated and recorded according to the guidelines of the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 (NCI-CTCAE). Patients who received less than 4 courses of treatment, patients with missing data, or patients who were scheduled for the 'Stop and Go strategy' therapy were excluded. The final study included 51 patients. Patients were categorized into two groups according to the frequency of peripheral neuropathy: the high-frequency group (high PN) or the low-frequency group (low PN). In this study, the frequency of peripheral neuropathy was defined as the value of the total expression of peripheral neuropathy during treatment divided by the total number of treatment courses. The median of the frequency of peripheral neuropathy was 0.40 (N = 51). Patients were equally divided by this median (0.40) into the high PN (median 0.60, 0.45-0.71, N = 27) and the low PN (median 0.19, 0.03-0.25, N = 24) groups. The study design was reviewed by a local ethics committee for research involving human subjects at the Graduate School of Pharmaceutical Sciences, North South University and South Dhaka Medical Center.

Data analysis: Information on gender; age; height; weight; Body Mass Index (BMI); Body Surface Area (BSA); type of cancer (rectum/colon/other); metastases (lung/liver/lymph node); surgical history; cancer chemotherapy history; radiotherapy history; chemotherapy regimen (mFOLFOX6/ mFOLFOX6+bevasizmab/FOLFOX4); oxaliplatin dose per course; number of cycles of chemotherapy that the

patient received; laboratory tests (total bilirubin (T. Bil), aspartate Aminotransferase (AST), alanine Aminotransferase (ALT), Lactate Dehydrogenase (LDH), Alkaline Phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), Blood Urea Nitrogen (BUN), Serum Creatinine (SCr), Na, K, Cl) and use of medication (antihypertensive, renin-angiotensin system inhibitor, Ca antagonist, narcoleptic, anti-microbial, anti-diabetic, anti-hyperlipidemic, laxative, prokinetic, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), anti-diarrheal, anti-peptic ulcer, anti-psychotropic, hematinic, narcotic and anti-flatulent agent) was obtained from the medical records. Variables were compared using the χ^2-test, Fisher's exact test and the Wilcoxon rank-sum test. For multivariate analysis, a Principal Component Analysis (PCA) and discriminant analysis were applied and predictive model equations were estimated. The level of statistical significance was set at $p<0.05$. All statistical analyses were performed using PASW software version 17 (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Frequency distribution of adverse events: The frequency distribution of adverse events is shown in Table 1. The maximum grade in all courses is presented as the grade for each patient. The incidence of adverse events was 88.2% for peripheral neuropathy, 49.0% for anorexia and 41.2% for nausea.

Peripheral neuropathy in the high-frequency group (high PN) and the low-frequency group (low PN): Table 2 shows the patient characteristics after patients were categorized to a high-frequency group of peripheral neuropathy (N = 27) and a low-frequency group of peripheral neuropathy (N = 24). Sex, age, BSA, type of cancer, metastatic status, past treatment history, type of regimen and the dose of oxaliplatin were not significantly different. The number of cycles of chemotherapy was significantly different (p = 0.002).

Laboratory tests and medications: Table 3 shows the patient characteristics with respect to their laboratory tests at baseline. The serum Chlorine (Cl) level of the high-PN group was approximately 2 mEq L^{-1} higher than that of the low PN group (p = 0.02). Other electrolytes and laboratory data were not significantly different. Table 4 shows the use of medication at baseline and there was no significant difference between the low PN and the high PN groups.

Factor analysis for predicting peripheral neuropathy: To identify the predicting factors from observed variables, PCA was performed using the method of factor extraction with PASW software. The variables Na, ALT and BSA were excluded because they overlapped with Cl, AST and oxaliplatin dose per course, respectively. Then, these variables were subjected to PCA. PCA revealed the presence of 15 components with eigenvalue exceeding 1, explaining 81.1% of the variance. To simplify the item structure, varimax rotation was used following principal components factor extraction. Table 5 shows the rotated

Table 1: Frequency distribution of adverse events (N = 51)

	Grading			
Adverse events	1	2	3	4
Peripheral neuropathy	6 (11.8)	17 (33.3)	23 (45.1)	5 (9.8)
Stomatitis	43 (84.3)	7 (13.7)	0 (0)	1 (2.0)
Fatigue	37 (72.5)	6 (11.8)	4 (7.8)	4 (7.8)
Anorexia	26 (51.0)	12 (23.5)	10 (19.6)	3 (5.9)
Nausea	30 (58.8)	10 (19.6)	6 (11.8)	5 (9.8)
Vomit	36 (70.6)	10 (19.6)	2 (3.9)	3 (5.9)
Diarrhea	39 (76.5)	9 (17.69	2 (3.9)	1 (2.0)
Constipation	38 (74.5)	12 (23.5)	1 (2.0)	0 (0)

*Data presented as n (%)

Table 2: Patient characteristics at baseline

Characteristics	Low PN (N = 24)	High PN (N = 27)	p-value
Male (%)	62.5	70.4	0.56
Age (years)*	59 (55-67)	64 (57-70)	0.16
Height (cm)*	160.8 (155.2-168.1)	162.5 (157.0-166.7)	0.82
Weight (kg)*	62.9 (55.6-66.4)	58.3 (49.1-66.0)	0.16
BMI (kg/m^2)*	23.9 (21.7-26.6)	22.6 (19.7-24.4)	0.08
BSA (m^2)*	1.61 (1.52-1.69)	1.57 (1.39-1.69)	0.29
Rectum/Colon/Other (%)	54.2/37.5/8.3	55.6/40.7/3.7	0.78
Metastasis (%)	75.0	85.2	0.29
Lung metastasis (%)	29.2	18.5	0.37
Liver metastasis (%)	45.8	66.7	0.13
Lymph node metastasis (%)	4.2	22.2	0.07
Surgical history (%)	91.7	92.6	1.0
Chemotherapy history (%)	25.0	14.8	0.49
Radiotherapy history (%)	4.2	0	0.47
Regimen (1/2/3)** (%)	79.2/12.5/8.3	77.8/14.8/7.4	0.97
Oxaliplatin dose per course (mg)*	130 (121-140)	130 (110-140)	0.51
Cycles patient received*	7 (5-9)	10 (8-12)	0.002

*Data presented as median (range). **Regimen 1, mFOLFOX6; regimen 2, mFOLFOX6+bevasizmab; regimen 3, FOLFOX4

Table 3: Patient characteristics for laboratory tests at baseline*

Characteristics	Low PN (N = 24)	High PN (N = 27)	p-value
T. bil. (mg dL^{-1})	0.58 (0.58-0.75)	0.55 (0.41-0.70)	0.61
AST (U L^{-1})	21 (17-36)	24 (17-29)	0.95
ALT (U L^{-1})	21 (14-40)	20 (13-30)	0.62
LDH (U L^{-1})	198 (157-284)	175 (151-201)	0.14
ALP (U L^{-1})	317 (222-471)	287 (184-423)	0.42
γ-GTP (U L^{-1})	38 (23-135)	40 (16-88)	0.62
BUN (mg dL^{-1})	12.2 (10.1-14.4)	10.8 (9.3-14.1)	0.39
SCr (mg dL^{-1})	0.77 (0.61-0.86)	0.65(0.57-0.76)	0.11
Na (mEq L^{-1})	141 (139-143)	141 (139-144)	0.52
K (mEq L^{-1})	4.4 (4.0-4.6)	4.2 (4.0-4.5)	0.42
Cl (mEq L^{-1})	104 (101-106)	106 (104-107)	0.02

*Data presented as median (range)

Table 4: Use of medication*

Medications	Low PN (N = 24)	High PN (N = 27)	p-value
Anti-hypertensive	6 (25.0)	11 (40.7)	0.23
RA system inhibitors	4 (16.7)	8 (29.6)	0.28
Ca antagonist	4 (16.7)	6 (22.2)	0.44
Narcoleptic	5 (20.8)	6 (22.2)	0.9
Anti-microbial	5 (20.8)	4 (14.8)	0.42
Anti-diabetic	0 (0)	2 (7.4)	0.28
Anti-hyperlipidemic	1 (4.2)	0 (0)	0.47
Laxative	7 (29.2)	9 (33.3)	0.75
Prokinetic	4 (16.7)	9 (33.3)	0.17
NSAIDs	9 (37.5)	5 (18.5)	0.13
Anti-diarrheal	2 (8.3)	2 (7.4)	0.65
Anti-peptic ulcer	9 (37.5)	8 (29.6)	0.55
Psychotropic	4 (16.7)	2 (7.4)	0.28
Hematinic	3 (12.5)	3 (11.1)	0.61
Narcotic	2 (8.3)	0 (0)	0.22
Anti-flatulent	3 (12.5)	3 (11.1)	0.61

*Data presented as n (%)

component matrix, representing the absolute value of factor loading in bold type if values were above 0.4 and in italic type if values were between 0.3 and 0.4.

Each principal component and major variable is summarized in Table 6. For example, principal component 1 comprised variables γ-GTP (0.863), ALP (0.856), AST (0.836), LDH (0.762), cecum cancer type (0.585), anti-hyperlipidemic agent (0.541) and psychotropic agent (0.470). Principal component 2 comprised the following variables: colon cancer type (0.964), rectum cancer type (-0.877) and psychotropic agent (0.418). Principal component 3 comprised the following variables: laxative agent (0.808), antibacterial agent (0.655), narcoleptic agent (-0.612), prokinetic agent (0.611) and age (0.424).

Regarding peripheral neuropathy, principal component 9 yielded a loading value of -0.776 for high PN (Table 5, 6). That is, it was suggested that variables such as Cl level and narcotic agent might be related to the incidence of peripheral neuropathy. BMI, liver metastasis and lymph node metastasis were also related to the incidence of peripheral neuropathy because each loading value was above 0.3. The positive factors for the incidence of peripheral neuropathy were serum Cl level, liver metastasis and lymph node metastasis. The use of a narcotic agent and BMI were negative factors.

Discriminant analysis of the model used to predict peripheral neuropathy: To build a predictive model for the group with a high frequency of peripheral neuropathy, the linear discriminant analysis was performed. Two models were generated for the integer-valued grouping variable of whether peripheral neuropathy appeared. Model equation A was based on the independent variable serum Cl level (Cl: mEq L^{-1}) and model equation B was derived from independent variables such as serum Cl level, usage of a narcotic agent (NA: yes = 1, no = 0), BMI (kg m^{-2}), the status of liver metastasis (LM: yes = 1, no = 0) and the status of lymph-node metastasis (LNM: yes = 1, no = 0). Each model was evaluated with cross-validation by the leave-one-out classification method.

Model equation A is:

$$z = (0.374 \times Cl)-39.075$$

Model equation B is:

$$z = (0.211 \times Cl)+(1.310 \times LM)+(1.734 \times LNM)+(-0.145 \times BMI) +(-1.090 \times NA)-19.608$$

Model equation A had a 60.9% prediction rate in classifying the presence of peripheral neuropathy. Model equation B had a 76.4% prediction rate. After the cross-validation, the rate of prediction success was 72.5%.

DISCUSSION

The primary purpose of this study was to investigate the predictive factors associated with the incidence of oxaliplatin-induced peripheral neuropathy, which is a major adverse event of oxaliplatin-base chemotherapy and is the most frequent dose-limiting toxicity in clinical practice. Peripheral sensory neuropathy is characterized by dysesthesia and/or distal paresthesia (fingers, toes and, less frequently, the peri-oral region and pharyngo-laryngeal tract) and induced or exacerbated cold. However, some patients treated with oxaliplatin show no or minimal peripheral neuropathy. These differences are poorly understood. In this study, 51 patients treated with the oxaliplatin-based regimen were retrospectively analyzed and peripheral neuropathy was observed in 45 patients (88.2%): 17 with grade 1 (33.1%), 23 with grade 2 (45.1%) and 5 with grade 3 (9.8%). Six patients did not complain of peripheral neuropathy. According to the frequency of peripheral neuropathy, patients were divided to two groups: high-frequency and low-frequency peripheral neuropathy. In the high PN group, serum Cl level at baseline and the total number of chemotherapy cycles were identified as predictive factors. However, the total number of chemotherapy cycles was not used because it was the variable used for assignment to the high PN and the low PN groups. Therefore, serum Cl level at baseline was identified as a predictive factor for the high PN group.

Oxaliplatin is normally administered by intravenous infusion and it is transformed essentially by water and nucleophiles such as Cl^- and HCO_3^- (Jerremalm *et al*., 2004). Thus, oxaliplatin, in contrast to cisplatin, should not be mixed with solutions containing chloride. The proposed principal mechanism of action of

Table 5: Rotated component matrix

	Component*														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
γ-GTP	**0.863**	-0.061	-0.051	0.036	0.198	-0.026	0.171	0.173	0.064	0.053	-0.075	-0.011	0.068	-0.062	0.012
ALP	**0.856**	0.046	-0.091	-0.223	0.076	-0.232	0	-0.062	-0.038	-0.026	-0.009	-0.043	-0.118	-0.031	-0.05
AST	**0.836**	0.21	0.248	0.121	-0.079	0.053	-0.044	-0.039	0.167	0.058	-0.07	-0.021	-0.082	0.036	-0.125
LDH	**0.762**	0.117	0.174	0.099	-0.209	-0.012	0.021	-0.063	0.02	-0.011	0.038	0.17	-0.098	0.057	-0.27
Cecum cancer	**0.585**	-0.146	-0.091	-0.18	*0.355*	0.208	0.065	*0.316*	-0.041	0.006	-0.137	-0.117	0.142	-0.005	0.299
Narcotic	**0.525**	*0.306*	0.216	0.179	-0.206	-0.076	-0.104	-0.246	**0.405**	0.058	0.016	-0.072	-0.05	-0.021	*-0.32*
Psychotropic	**0.47**	**0.418**	-0.096	0.272	0.056	0.103	0.22	0.086	0.299	0.054	*0.31*	-0.096	-0.13	0.259	-0.129
Colon cancer	-0.014	**0.964**	0.048	-0.06	-0.001	0.026	-0.038	-0.017	-0.028	0.032	-0.024	0.004	0.013	-0.006	-0.061
Rectum cancer	-0.262	**-0.88**	-0.004	0.144	-0.167	-0.124	0.007	-0.132	0.046	-0.034	0.089	0.051	-0.08	0.008	-0.081
Laxative	0.217	0.057	**0.808**	0.017	0.134	0.003	0.116	0.092	-0.024	0.068	0.044	-0.045	0.023	-0.043	-0.017
Antibacterial	-0.064	0.024	**0.655**	0.065	0.06	-0.037	-0.025	-0.168	0.134	-0.003	**0.444**	-0.01	*0.335*	-0.025	0.055
Narcoleptic	-0.119	0.011	**-0.61**	0.165	0.209	0.008	-0.116	0.103	0.043	*0.368*	0.143	-0.266	0.038	-0.077	-0.069
Prokinetic	-0.251	-0.074	**0.611**	0.128	0.148	0.153	-0.065	0.008	-0.13	0.25	0.079	-0.217	-0.099	-0.283	0.08
Age	0.145	0.227	**0.424**	-0.051	*0.368*	0.141	0.156	*0.369*	-0.288	0.243	-0.08	0.172	-0.182	0.099	-0.194
Regimen 2	-0.001	0.11	-0.054	**-0.93**	-0.006	0.029	0.069	-0.022	0.009	0.077	-0.149	-0.025	-0.055	-0.005	-0.063
Regimen 1	0.047	-0.031	-0.019	**0.84**	-0.04	-0.097	-0.035	0.06	-0.001	-0.107	**-0.47**	0.004	0.05	0.052	0.026
Hematinic	-0.003	-0.201	-0.126	0.128	**-0.74**	0.128	0.049	0.294	-0.06	-0.028	-0.068	0.099	-0.022	-0.006	0.041
BUN	0.141	-0.017	0.095	0.111	**0.653**	-0.031	0.152	0.202	0.07	0.15	0.082	0.27	-0.087	0.167	-0.063
Sex	-0.248	0.191	-0.007	-0.201	-0.131	**0.769**	0.007	-0.018	0.163	-0.107	0.063	-0.193	0.006	-0.022	0.148
Oxaliplatin dose	-0.209	-0.031	-0.053	-0.118	-0.128	**-0.67**	-0.245	-0.056	0.286	0.065	-0.15	0.119	0.216	-0.009	0.137
Anti-peptic ulcer	0	-0.155	0.043	0.025	*-0.31*	**0.562**	-0.264	0.095	0.207	-0.055	0.055	0.288	0.065	0.017	0.046
Cl	-0.203	0.204	0.047	-0.047	0.101	**0.529**	-0.092	0.065	**-0.44**	0.117	-0.083	-0.06	*0.361*	-0.111	0.074
T.Bil.	0.111	0.015	0.133	-0.084	-0.072	-0.067	**0.858**	0.13	0.2	0.071	0.018	-0.065	-0.035	0.069	0.119
Lung meta	-0.044	-0.064	0.086	-0.15	0.299	0.085	**0.636**	-0.291	-0.05	0.196	-0.108	0.231	*-0.31*	-0.04	0.113
Anti-hyperlipidemic	**0.541**	-0.093	-0.025	0.069	0.278	0.076	**0.564**	0.362	-0.018	-0.085	0.032	0.002	0.103	-0.004	0.111
Ca antagonist	0.052	0.057	0.007	0.094	-0.082	0.088	0.011	**0.876**	0.007	0.043	-0.11	-0.08	-0.195	-0.097	0.095
High PN	-0.131	0.048	0.065	0.025	-0.075	-0.035	-0.123	0.027	**-0.78**	0.087	0	-0.185	-0.042	0.074	-0.02
BMI	0.012	0.206	0.108	-0.37	0.145	-0.104	0.199	0.267	0.391	0.239	0.309	-0.073	0.135	0.054	0.245
Anti-diarrheal	-0.112	-0.162	-0.145	0.091	-0.081	-0.016	-0.047	-0.014	0.064	**-0.85**	-0.025	-0.081	-0.118	-0.053	0.128
Anti-flatulent	0.047	0.113	0.096	0.148	-0.024	0.174	-0.12	-0.04	0.027	**-0.75**	-0.082	-0.063	-0.083	-0.038	*-0.38*
Regimen 3	-0.071	-0.094	0.097	-0.095	0.068	0.111	-0.035	-0.064	-0.009	0.065	**0.908**	0.025	-0.007	-0.074	0.041
Past RadioT	-0.067	-0.073	-0.093	0.075	0.108	0.026	-0.025	-0.065	0.17	0.101	-0.119	**0.77**	-0.034	-0.093	0.008
Past ChemoT	0.129	0.117	0.202	-0.303	*-0.32*	-0.216	-0.045	-0.026	0.021	0.057	0.279	**0.61**	0.183	0.051	0.071
SCr	-0.03	-0.047	-0.021	0.187	*0.376*	*-0.34*	0.219	0.032	-0.008	-0.084	0.216	**0.535**	0.184	0.193	0.07
NSAIDs	-0.008	-0.073	0.144	-0.031	0.132	0.048	-0.17	-0.179	0.259	0.106	-0.028	0.221	**0.737**	-0.017	-0.016
Lymph node Meta	-0.106	0.16	-0.034	0.124	-0.237	-0.088	0.008	-0.019	*-0.32*	0.111	0.102	-0.101	**0.652**	-0.109	0.098
Liver Meta	*0.393*	-0.06	0.201	-0.115	0.031	-0.007	*-0.31*	0.161	*-0.33*	-0.261	0.189	-0.005	**-0.42**	0.141	0.139
Anti-diabetic	-0.137	0.124	-0.139	0.156	0.109	-0.137	0.093	-0.084	-0.103	0.143	0.017	-0.079	-0.112	**0.767**	0.044
K	0.179	*-0.35*	0.05	-0.101	0.071	0.226	-0.159	-0.027	0.113	-0.094	-0.248	0.064	-0.057	**0.681**	0.022
RA system Inh.	0.021	0.211	-0.056	-0.199	-0.039	-0.168	0.201	0.516	-0.207	0.015	0.15	0.042	0.107	**0.516**	-0.283
Past Ope.	-0.22	0.017	0.081	0.097	-0.098	0.068	0.161	0.034	0.009	0.072	0.056	0.064	0.019	0	**0.87**
Eigenvalues	5.59	3.61	3.04	2.94	2.47	2.31	2.02	1.79	1.72	1.65	1.53	1.28	1.17	1.09	1.02
Contribution ratio (%)	13.63	8.82	7.42	7.18	6.03	5.64	4.93	4.36	4.2	4.01	3.73	3.13	2.86	2.67	2.5
Cumulative contributionratio (%)	13.63	22.45	29.87	37.05	43.08	48.72	53.65	58.01	62.21	66.22	69.96	73.09	*75.95*	78.62	81.11

*The absolute value of factor loading in bold type if values were above 0.4 and in italic type if values were between 0.3 and 0.4 and under line show negative factor

Table 6: Principal components and major variables

Principal components	Variables*
1	γ-GTP, ALP, AST, LDH, Cecum cancer, Narcotic, Psychotropic, Anti-hyperlipidemic, *Liver meta*
2	Colon cancer, Rectum cancer, Psychotropic, *K*, *Narcotic*
3	Laxative, Anti-bacterial, Narcoleptic, Prokinetic, Age
4	Regimen 2, Regimen 1, *BMI*
5	Hematinic, BUN, *SCr, Age, Cecum cancer, Past Chemotherapy, Anti-peptic ulcer*
6	Sex, Oxaliplatin dose, Anti-peptic ulcer, Cl, *SCr*
7	T. Bil, Lung meta, Anti-hyperlipidemic, *Liver meta*
8	Ca antagonist, *Age*, *Anti-hyperlipidemic*, *Cecum cancer*
9	High PN, Cl, Narcotic, *BMI*, *Liver meta*, *Lymph node meta*
10	Anti-diarrheal, Anti-flatulent, *Narcoleptic*
11	Regimen 3, Regimen 1, Antibacterial, *Psychotropic*, *BMI*
12	Past radiotherapy, Past chemotherapy, SCr
13	NSAIDs, Lymph node meta, Liver meta, *Cl*, *Antibacterial*, *Lung meta*
14	Anti-diabetic, K, RA system inhibitor
15	Past operation, *Anti-flatulent*, *Narcotic*

*The absolute value of factor loading in bold type if values were above 0.4 and in italic type if values were between 0.3 and 0.4 in Table 5. Underlined variables show negative factors as shown in Table 5

oxaliplatin is the formation of platinum-DNA adducts, resulting in cell death (Mani *et al*., 2002). Oxaliplatin degradation in aqueous media depends on the chloride concentration and the pH (Alberto *et al*., 2008; Jerremalm *et al*., 2004). The major biotransformation products from oxaliplatin in the presence of chloride are [Pt (1,2-diaminocyclohexyl) Cl_2] (dichloro complex) and oxalate (Alberto *et al*., 2008). The dichloro complex has been shown to be more cytotoxic than oxaliplatin *in vitro* (Luo *et al*., 1998). Oxaliplatin altered voltage-gated Na^+ channel kinetics on rat sensory neurons (Adelsberger *et al*., 2000). Grolleau *et al*., 2001 showed that oxaliplatin is capable of altering the voltage-gated Na^+ channels through a pathway involving calcium ions, which are probably immobilized by the oxalate (Grolleau *et al*., 2001). Recently, Sakurai *et al*. (2009) showed that oxalate is involved in oxaliplatin-induced cold hyperalgesia/ allodynia but not mechanical allodynia through the chelation of Ca^{2+} and Mg^{2+}. However, the dichloro complex induces mechanical allodynia but not cold hyperalgesia/allodynia (Sakurai *et al*., 2009). The degradation of oxaliplatin might be affected by the high serum Cl level and the resulting oxalate might be involved in the incidence of peripheral neuropathy. Therefore, monitoring the serum Cl level in patients might be useful in predicting peripheral neuropathy.

CONCLUSIONS

Retrospective analysis indicates that the serum Cl level at baseline, use of a narcotic agent, BMI, status of liver metastasis and status of lymph node metastasis are predictive factors for peripheral neuropathy associated with the administration of oxaliplatin. Our predictive model equation achieved 60.9% and 76.4% prediction rates. This equation may be useful for predicting the incidence of peripheral neuropathy in clinical practice. Understanding the patient's characteristics could be useful in predicting and preventing oxaliplatin-induced peripheral neuropathy.

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