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Predicting Acute and Persistent Neuropathy Associated with Oxaliplatin

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Abstract

Objectives—We sought to predict oxaliplatin-associated peripheral neuropathy during modified FOLFOX6 (mFOLFOX6) therapy.

Methods—In a 50% female sample, patients with previously untreated, primary or recurrent colorectal cancer were followed through a first course of mFOLFOX6 with oxaliplatin 85 mg/m² every 2 weeks. Accounting for correlation among a subject's cycles, logistic regression estimated per-cycle risk of acute (under 14 days) and persistent (14 days or more) neuropathy. Proportional hazards regression predicted time to persistent neuropathy.

Results—Among mFOLFOX6 recipients (n=50, age 58.9 +10.1 years), 36% received concomitant bevacizumab. Of total cycles, 94.2% (422/448) were evaluable. Most (84%) subjects reported neuropathy at least once: 74% reported acute and 48% reported persistent symptoms. On multivariate analysis, risk factors shared by acute and persistent neuropathy were body-surface area >2.0, acute neuropathy in a past cycle, and lower body weight. In addition, risk of acute neuropathy decreased with age (adjusted for renal function and winter season), while risk of persistent neuropathy increased with cumulative dose of oxaliplatin and persistent neuropathy in a past cycle. Concomitant bevacizumab was not a risk factor when administered in Stage IV disease but was associated with persistent neuropathy when administered experimentally in Stage III. Females had no increased risk of either form of neuropathy. After 3 cycles, weight, body-surface area, and prior acute neuropathy predicted time to persistent neuropathy.

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Conclusions—Routinely available clinical factors predict acute and persistent neuropathy associated with oxaliplatin. When validated, the proposed prognostic score for persistent neuropathy can help clinicians counsel patients about chemotherapy.

Key Words (MeSH)

Peripheral Nervous System Diseases/chemically induced; Risk Factors; Chemotherapy; Adjuvant; Organoplatinum Compounds/adverse effects; Colonic Neoplasms/drug therapy

Introduction

Although all platinum analogs are potentially neurotoxic, oxaliplatin is associated with a unique spectrum of neurologic symptoms [1]. Axonal membrane sodium channel dysfunction, characterized by reduced sensory axonal excitability [1,2], occurs immediately after infusion and is usually accompanied by acute symptoms, including transient paresthesia and muscular spasms in the limbs and perioral region [3]. Acute symptoms may be induced by touching or drinking cold items [3]. At greater cumulative doses, progressive abnormalities develop in sensory axonal excitability [2] and are often accompanied by symptoms of persistent neurotoxicity, specifically sensory dysfunction with distal paresthesia that may progress to sensory ataxia and functional impairment that may persist long-term [3-6]. Research to establish safe and effective prophylaxis against oxaliplatin's neurotoxicity is ongoing [7-9].

If patients at increased risk of oxaliplatin-associated neuropathy could be identified, they might be offered alternative regimens without oxaliplatin. However, currently there is no validated method for distinguishing high-risk patients. It has been observed that the probability and severity of neurotoxicity increase with cumulative dose of oxaliplatin [10]. Risk of neuropathy has also been proposed to vary by treatment schedule and duration of infusion [11] and by concomitant use of NSAIDs [12]. In addition, three studies have variously associated genetic polymorphisms of glutathione S-transferase P1 (*GSTP1*) with Grade 3 neurotoxicity [13,14] or neurotoxicity-associated discontinuation of FOLFOX [15]. However, due to lack of consensus across the 3 studies, there is as yet no established marker for genetic susceptibility to oxaliplatin-associated neuropathy.

To identify risk factors that would be routinely available in the clinical setting, we assembled a cohort of patients with colorectal cancer who received a first course of modified FOLFOX6 (mFOLFOX6) that included oxaliplatin. The outcome of primary interest was persistent neuropathy, because of its contribution to early discontinuation of oxaliplatin-based regimens [13-15].

Materials and Methods

Subjects were consecutive patients with colorectal cancer who began a first course of mFOLFOX6 at our center between March 2006 and September 2009. Patients who received concomitant therapies other than bevacizumab 5 mg/kg were excluded. A retrospective chart review was conducted with the approval of the hospital's Institutional Review Board, which

granted a waiver of informed consent to ensure that consecutive eligible subjects, even those deceased or lost to follow-up, could be included.

Oxaliplatin was administered as a 2-hour intravenous infusion every 2 weeks at a dose of 85 mg per meter squared (m^2) of body-surface area (BSA, based on actual body weight and height [16]). Reduction in oxaliplatin dose was uncommon, usually of 20-25%, and did not disqualify the cycle from being studied. Prophylaxis against persistent neuropathy was at the physician's discretion.

Subjects were followed retrospectively until they completed the prescribed course (up to 12 cycles were studied) or discontinued mFOLFOX6 or oxaliplatin for: surgical treatment; disease progression or lack of response; toxicity or poor tolerability. Study follow-up was censored when mFOLFOX6 was discontinued for purely logistical reason.

Outcome per cycle was acute or persistent neuropathy, defined according to the oxaliplatin label [17] and documented in the medical record. In brief, neuropathy (paresthesia, dysesthesia, and/or hypoesthesia typically in the hands, feet, perioral area, or throat) was labeled acute (duration less than 14 days) or persistent (duration at least 14 days). Cycles without sufficient symptom documentation were nonevaluable for the analysis of neuropathy per cycle but were retained for the calculation of cumulative incidence of treatment endpoints.

Risk factors that could vary by cycle were cumulative dose of oxaliplatin (in mg/m^2), body weight, BSA, body mass index (BMI), calculated creatinine clearance, dose of bevacizumab, season (winter was defined as December-February), history of acute and history of persistent neuropathy in a past cycle. Risk factors that were constant across cycles included age and stage of disease at start of treatment, sex, height, and preexisting diabetes or neuropathy.

Cycles with acute neuropathy and cycles with persistent neuropathy were compared to cycles without neuropathy. Risk factors were evaluated in univariate analysis using Fisher's exact test (2-sided, significance at $p < 0.10$) and in multivariate analysis using logistic regression models fit by generalized estimating equations (GEE), with covariates and their potential interactions retained if they improved the model's fit to the observed data, as indicated by the quasi-likelihood information criterion [18]. Because the study was exploratory, p values were not adjusted for multiple hypothesis testing. Models were binomial with autoregressive correlation structure to take into account correlation within each subject's series of cycles. The influence of individual subjects (specifically, their clusters of cycles) was measured using dfbeta statistics developed for models fit to correlated data by GEE [19]. Similar methodology was used to compare nonevaluable versus evaluable cycles and recipients versus nonrecipients of bevacizumab.

A landmark analysis after 1, 2, or 3 cycles was used to determine the optimal time to evaluate a patient's risk of persistent neuropathy. For the landmark analysis, cycles without symptom documentation were assumed to have been free of neuropathy. Proportional hazards regression, with history of acute neuropathy evaluated at the landmark, was used to predict time to onset of persistent neuropathy. The assumption of proportionality of hazards was verified in graphical analysis.

Results

Subjects

Among our subjects (n=50, age 33-78 years, Table 1), 18 (36%) received concomitant bevacizumab, which was prescribed to most (16/25, 64%) subjects with Stage IV but to few (2/23, 8.7%) subjects with Stage III disease. In Stage IV cases, bevacizumab was more likely to be used in subjects less than 50 years of age (O.R. 5.15, 95% C.I. 1.24-21.42). Six (12%) subjects had preexisting neuropathy or pain from: injury to back or arm (n=3), multiple sclerosis (n=2), or fibromyalgia (n=1).

By Kaplan-Meier analysis, median duration of mFOLFOX6 therapy was 10 cycles. Censoring of follow-up for logistical reasons occurred in 2 cases: 1 subject relocated out of the area, and another was unable to care for his central line. At close of follow-up, the cumulative incidence was 46.1% ($\pm 7.3\%$) completion of cycles prescribed, 27.0% ($\pm 6.4\%$) discontinuation for toxicity or tolerability, 14.6% ($\pm 5.1\%$) discontinuation for disease progression or lack of response, and 12.4% ($\pm 4.8\%$) discontinuation for surgical treatment. Among subjects who discontinued for toxicity or tolerability (n=13), 6 had reported acute and persistent neuropathy during treatment, 4 others had reported acute neuropathy only, and another 3 had reported persistent neuropathy only.

Subjects received a total of 448 cycles, of which 94.2% (n=422) had sufficient documentation to be evaluable for neuropathy. A cycle's likelihood of evaluability increased with the subject's apparent vulnerability to toxicity. Specifically, evaluability increased with lower body weight (Odds Ratio (O.R.) 7.51, 95% C.I. 2.85-19.83, per step decrease from 90-120 to 60-89 to <60 kg) and greater age (O.R. 1.65, 1.02-2.66, per increase from 33-49 to 50-59 to 60-69 to 70-78 years). At the same time, evaluability was more common with obesity (BMI at least 30: O.R. 3.84, 1.37-10.76), preexisting neuropathy (O.R. 4.48, 0.90-22.42), and concomitant use of bevacizumab (O.R. 3.91, 0.83-18.48). Evaluability did not vary according to which physician dictated the clinical notes (data not shown).

Neuropathy

Figure 1 shows the frequency of acute and persistent neuropathy reported by cycle. As shown, there was considerable attrition of subjects over time, partially attributable to toxicity and tolerability, which limited the percentage (maximum 57%) who reported either form of neuropathy in any one cycle. Overall, however, 84% of subjects reported neuropathy at least once: acute and persistent neuropathy were reported by 74% and 48% of subjects, respectively. Neuropathy of either type was generally of Grade 1 or 2, but 6 (12%) subjects reported Grade 3 neuropathy at or beyond the eighth cycle, specifically in 7/102 (6.9%) cycles at a cumulative oxaliplatin dose of 675 mg/m² or higher.

In 3 subjects, persistent neuropathy was atypical: it occurred early (during cycle 1, 2, or 3) and without prior acute neuropathy. The case in cycle 1 began as jaw discomfort immediately after oxaliplatin administration, followed in the same cycle by persistent neuropathy in the lower extremities. The case that began in cycle 2 progressed from the feet to midcalf in a single cycle, then persisted through multiple cycles. Lastly, the case of

persistent neuropathy that began in cycle 3 affected hands and feet but was mild until cycle 10, when it reached Grade 3.

Univariate Analysis of Neuropathy

Cumulative exposure to oxaliplatin, whether measured by cycle or dose, was more strongly associated with persistent than with acute neuropathy (Fig. 1 and Table 2). Further univariate analysis suggested that lower body weight, absence of preexisting neuropathy or diabetes, and acute neuropathy in a past cycle were potential risk factors for both acute and persistent neuropathy; female sex, younger age, and BSA >2.0 were potentially associated with acute neuropathy; and greater BMI and persistent neuropathy in a past cycle were potentially associated with persistent neuropathy (Table 2). On univariate analysis, stage of disease, height, creatinine clearance, concomitant bevacizumab, magnesium-calcium as therapy or prophylaxis, and wintertime treatment were not associated with either form of neuropathy (Table 2).

Multivariate Analysis of Neuropathy

On multivariate analysis (Table 3), risks of acute and persistent neuropathy per cycle were associated with BSA >2.0 and acute neuropathy that occurred in a past cycle and were inversely associated with body weight. In addition, risk of acute neuropathy decreased continuously with age, an effect impossible to detect until renal function and season of treatment were taken into account. In contrast, risk of persistent neuropathy increased continuously with cumulative dose of oxaliplatin and persistent neuropathy in a past cycle. The only risk factor that differed by the patient's stage of disease was bevacizumab, which increased the risk of persistent neuropathy when it was used experimentally in Stage III, but not in Stage IV disease. Neither acute nor persistent neuropathy was independently associated with sex, BMI, height, preexisting neuropathy or diabetes, stage of disease, or use of magnesium-calcium.

Prognostic Score for Persistent Neuropathy

For the purpose of prognosis, the optimal time to assess a patient's risk of developing persistent neuropathy was after 3 cycles of mFOLFOX6 (data not shown). In other words, survival without persistent neuropathy was best predicted by status at the start of cycle 4, when 45 (90%) subjects were still in treatment and had not yet experienced persistent neuropathy. Independent predictors were weight, BSA >2.0, and history of acute neuropathy during the first 3 cycles (Table 4). To illustrate, survival without persistent neuropathy was univariately stratified by history of acute neuropathy during cycles 1-3 (Figure 2a) and by weight (Figure 2b). Survival without persistent neuropathy is not shown by BSA, however, because the effect of BSA could not be detected until the confounding effects of weight and prior acute neuropathy were controlled in multivariate analysis (Table 4).

A prognostic score of 0-3 points was derived from the model of risk of persistent neuropathy in Table 4, as follows. Immediately before cycle 4, subjects who had not yet developed persistent neuropathy were assigned a point each for history of acute neuropathy and BSA >2.0 and either 1 point for intermediate weight (60-89 kg) or 2 points for low weight (46-59

kg). The distribution of prognostic scores is shown together with corresponding survival without persistent neuropathy (Figure 2c).

Discussion

The current study of oxaliplatin-associated neuropathy identified several novel risk factors for acute and persistent neuropathy. These routinely available, clinical risk factors were independent of cumulative dose of oxaliplatin, which we found to be continuously associated with the risk of persistent (but not acute) neuropathy. No threshold or plateau was detected in the dose effect of oxaliplatin.

We translated our findings on risk of persistent neuropathy into a straightforward prognostic score that awaits validation in a large, multicenter patient registry or clinical trial database. Our prognostic score is optimally assessed after 3 cycles of oxaliplatin. However, it is possible to utilize the score even before treatment with oxaliplatin, by calculating the patient's score twice: once assuming that acute neuropathy would not develop during the first 3 cycles and a second time assuming instead that it would develop. The persistent neuropathy-free survival curves that correspond to these 2 scores would then describe the patient's 2 possible prognoses, depending on whether acute neuropathy develops early or not. We found that it was not possible to predict persistent neuropathy that occurred before cycle 4, because such events occurred rarely (in 3 of 141 evaluable early cycles) and were atypical.

In our study, we observed that the greater the body weight, the lower the risk of acute and persistent neuropathy, a finding consistent with the fact that oxaliplatin is cleared initially via distribution into the tissues [20,21]. In contrast to weight, height was not an informative factor; as a result, BMI (weight adjusted for height) did not predict neuropathy as efficiently as weight alone did. We also observed that high BSA ($>2.0 \text{ m}^2$) increased the risk of both forms of neuropathy. This association was independent of body weight, height, and cumulative dose and may represent the risk associated with receiving a very large dose of oxaliplatin at once during the cycle. In addition, we observed that acute neuropathy in a past cycle was predictive of both acute and persistent neuropathy, a finding that suggests that history of acute neuropathy may indicate a genetic predisposition to neurotoxicity with exposure to oxaliplatin. Persistent neuropathy in a past cycle was predictive of its recurrence in subsequent cycles.

After adjustment for season and creatinine clearance, we found that with increasing age, patients were less likely to report acute neuropathy. Treatment during winter months, even in our milder climate, was associated with a near doubling in the risk of acute neuropathy; although this association fell just short of statistical significance, it was consistent with the concept of cold-induced neuropathy [3]. Reflecting oxaliplatin's ultimate clearance by glomerular filtration [20,21], normal renal function was associated with lower risk of acute neuropathy; this association, too, fell just short of statistical significance. Although renal dysfunction has been previously associated with plasma availability of unbound platinum [21], prior studies have not detected an increase in oxaliplatin-associated neuropathy with renal impairment [21,22]. However, those studies observed their subjects only briefly

(during the first 1 or 2 cycles of oxaliplatin), did not differentiate between acute and persistent neuropathy, and lacked sufficient sample size to support a multivariate analysis. According to the current study, renal dysfunction promotes acute but not persistent neuropathy; the mechanism for this specificity is unclear.

In our study, concomitant bevacizumab did not affect the risk of acute neuropathy and only increased the risk of persistent neuropathy when prescribed experimentally to patients with Stage III disease, a finding that may have resulted from patient selection rather than from the drug itself. Previously, an association between bevacizumab and grade 3-4 neuropathy has been reported [23] but not confirmed [24].

The ideal study of neuropathy would be conducted prospectively, using a validated questionnaire. The current study was conducted retrospectively, but it was free of two sources of bias commonly found in retrospective studies. Selection bias was avoided, because consecutive eligible patients were studied, over 94% of cycles were evaluable, and factors associated with evaluability were controlled as necessary in the statistical analyses. Recall bias was avoided, because all data were recorded by the treating physician at the start and close of each cycle. Neuropathy was detected in 84% of subjects. The possibility of patient underreporting or physician underrecording of neurologic symptoms cannot be ruled out, but any underascertainment of neuropathy likely arose at random and thus was unlikely to have caused the models to yield biased results. Under the definitions of acute and persistent neuropathy used in the study, some cases commonly regarded as acute neuropathy could have been categorized as persistent, ie, when a case of cold-induced neuropathy persisted beyond 14 days.

Our study was limited to data routinely generated during clinical practice at a single center. We studied over 400 cycles at risk of neuropathy but did not have sufficient sample size to set aside half our subjects' data for validation of the models and prognostic score. Thus, current findings are preliminary until confirmed in a separate sample.

Despite its limitations, our study was able to show for the first time that, independently of cumulative dose of oxaliplatin, routinely available patient characteristics help to explain variability in the risk of neuropathy, both acute and persistent, during treatment with an oxaliplatin-containing regimen. Our study also yielded a novel prognostic score for oxaliplatin-associated persistent neuropathy, offering clinicians a practical means to identify patients at greater risk of persistent neuropathy, in order to counsel them about this toxicity and discuss options that may reduce its incidence: the OPTIMOX strategy [31,32], neuroprotective agents under development [33,34], or a similarly efficacious regimen without oxaliplatin (FOLFIRI: 5-fluorouracil, leucovorin, irinotecan) [30]. Finally, the methodology we used and the risk factors we identified can inform future studies, especially those evaluating oxaliplatin-containing regimens [23,24] or neuroprotective agents [9,10,33,34] or validating genetic markers for susceptibility to neurotoxicity [13-15]. After validation, the prognostic score we have proposed could be utilized to stratify randomization to treatment or prophylaxis in clinical trials that will assess neurotoxicity.

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Fig. 1.
Frequency of Acute and Persistent Neuropathy, By Cycle of mFOLFOX6 (N=422).

Fig. 2.

Survival Free of Persistent Neuropathy In Subjects after 3 Cycles of mFOLFOX6 (N=45), Stratified by a) History of Acute Neuropathy Prior to Cycle 4, b) Weight Prior to Cycle 4, and c) Prognostic Score Assessed Prior to Cycle 4.

Footnotes: to Fig. 2a) Log-Rank test, $p < 0.01$.

to Fig. 2b) $p < 0.01$.

to Fig. 2c) $p < 0.0001$. Immediately before cycle 4, subjects who had not yet developed persistent neuropathy were assigned a point each for history of acute neuropathy and BSA > 2.0 and either 1 point for intermediate weight (60-89 kg) or 2 points for low weight (46-59 kg).

Table 1

Characteristics of Subjects at Initiation of mFOLFOX6 Therapy (n=50).

	N (%)	Mean (Std Dev)
Male	25 (50)	
Age, years		58.9 (10.1)
Stage of Disease		
II (High Risk subset)	2 (4)	
III	23 (46)	
IV	25 (50)	
Comorbidity		
Diabetes Mellitus *	6 (12)	
Non-diabetic Neuropathy	6 (12)	
Neither	38 (76)	
BMI		26.9 (5.2)
Calculated Creatinine Clearance, mL/s/m ²		
In Males		1.37 (0.32)
In Females		0.96 (0.25)
BSA, m ²		
In Males		1.99 (0.16)
In Females		1.73 (0.23)
Weight, kg		
In Males		83.9 (14.2)
In Females		69.1 (16.8)
Height, cm		
In Males		175.7 (7.3)
In Females		160.9 (7.3)

* No subject had evidence of preexisting diabetic neuropathy.

Table 2
Univariate Analysis: Frequency of Acute and Persistent Neuropathy, By Characteristics of Cycles (N=422).

Cycle Characteristics	Neuropathy			
	None N (%)	Acute N (%)	Persistent N (%)	<i>p</i> [*]
Sex				0.494
Female	111 (44.9)	61 (57.0)	34 (50.0)	
Male	136 (55.1)	46 (43.0)	34 (50.0)	
Age				0.496
Under 60 Years	126 (51.0)	70 (65.4)	38 (55.9)	
60 Years and Older	121 (49.0)	37 (34.6)	30 (44.1)	
Stage of Disease				0.586
II-III	121 (49.0)	50 (46.7)	36 (52.9)	
IV	126 (51.0)	57 (53.3)	32 (47.1)	
Weight, kg				0.007
46-59	21 (8.5)	19 (17.8)	11 (16.2)	
60-89	180 (72.9)	64 (59.8)	52 (76.5)	
90-120	46 (18.6)	24 (22.4)	5 (7.4)	
Height, cm				0.570
<160	59 (23.9)	26 (24.3)	14 (20.6)	
160-179	153 (61.9)	61 (57.0)	41 (60.3)	
180+	35 (14.2)	20 (18.7)	13 (19.1)	
Body Mass Index				0.0003
<25	71 (28.7)	39 (36.5)	31 (45.6)	
25-<30	89 (36.0)	32 (29.9)	29 (42.7)	
30 and up	87 (35.2)	36 (33.6)	8 (11.8)	
Body-Surface Area, m ²				0.260
Up to 2.0	192 (77.7)	66 (61.7)	48 (70.6)	
> 2.0	55 (22.3)	41 (38.3)	20 (29.4)	
Creatinine Clearance, mL/s/m ²				0.347
1.33	55 (22.3)	24 (22.4)	22 (32.4)	

Cycle Characteristics	Neuropathy			
	None N (%)	Acute N (%)	Persistent N (%)	<i>p</i> [*]
1.00-1.32	61 (24.7)	34 (31.8)	14 (20.6)	
<1.00	77 (31.2)	26 (24.3)	21 (30.9)	
Unknown	54 (21.9)	23 (21.5)	11 (16.2)	
Cumulative Oxaliplatin,mg/m ²				<0.0001
Under 250	80 (32.4)	17 (15.9)	3 (4.4)	0.005
250-<500	78 (31.6)	43 (40.2)	15 (22.1)	
500-<750	58 (23.5)	36 (33.6)	22 (32.4)	
750 and Over	31 (12.6)	11 (10.3)	28 (41.2)	
Concomitant Bevacizumab				0.389
Yes	88 (35.6)	33 (30.8)	20 (29.4)	
No	159 (64.4)	74 (69.2)	48 (70.6)	
Magnesium-Calcium				0.260
Yes	7 (2.8)	7 (6.5)	4 (5.9)	
No	240 (97.2)	100 (93.5)	64 (94.1)	
Winter (December-February)				0.370
Yes	47 (19.0)	27 (25.2)	9 (13.2)	
No	200 (81.0)	80 (74.8)	59 (86.8)	
Comorbidity				0.0003
Diabetes Mellitus	39 (15.8)	12 (11.2)	5 (7.2)	
Non-diabetic Neuropathy	37 (15.0)	7 (6.5)	1 (1.5)	
Neither	171 (69.2)	88 (82.2)	62 (91.2)	
Acute Neuropathy, Past Cycle				<0.0001
Yes	55 (22.3)	70 (65.4)	51 (75.0)	
No	192 (77.7)	37 (34.6)	17 (25.0)	
Persistent Neuropathy, Past Cycle				<0.0001
Yes	14 (5.7)	6 (5.6)	38 (55.9)	1.000
No	233 (94.3)	101 (94.4)	30 (44.1)	

* Compared to subjects without neuropathy of either type.

Table 3

Risk Factor	Acute Neuropathy Model (Cases N=107, Controls N=247)		Persistent Neuropathy Model (Cases N=68, Controls N=247)	
	Odds Ratio (95% CI)	p	Odds Ratio (95% CI)	p
Cumulative Oxaliplatin, per additional 85 mg/m ²	---	---	1.27 (1.05 – 1.53)	0.0003
Body-Surface Area				
Above 2.0 m ²	4.61 (1.94 – 10.95)	0.0005	8.74 (1.79 – 42.71)	0.007
Not Above 2.0 m ²	1.00		1.00	
Weight, per additional kilogram	0.97 (0.95 – 0.99)	0.013	0.93 (0.89 – 0.98)	0.008
Age, per additional year	0.97 (0.95 – 0.99)	0.012	---	---
Season of Treatment				
Winter	1.80 (0.97 – 3.36)	0.063		
Not Winter	1.00		---	---
Renal Function (Creatinine Clearance, mL/s/m ²)				
Normal (At least 1.33)	0.59 (0.32 – 1.06)	0.078		
Impaired (<1.33)	1.00			
Not Tested at Start of Cycle	1.00			
Concomitant Bevacizumab	---	---		
Yes, Stage III Disease			113.7 (38.3 – 337.5)	<0.0001
Yes, Stage IV Disease			0.62 (0.24 – 1.59)	0.32
No			1.00	
Acute Neuropathy in a Past Cycle				
Yes	4.49 (2.67 – 7.54)	<0.0001	5.73 (2.17 – 15.11)	0.0004
No	1.00		1.00	
Chronic Neuropathy in a Past Cycle	---	---		
Yes			8.35 (1.96 – 35.51)	0.004
No			1.00	

Table 4

Multivariate Analysis: Predictors of Persistent Neuropathy among Recipients of mFOLFOX6 Followed from Fourth Cycle Onward (N=45).

Characteristics at Start of Cycle 4	Hazards Ratio (95% CI)	<i>p</i>
Body-Surface Area, m ²		
Greater than 2.0	9.06 (1.83 – 44.92)	0.007
2.0 or Less	1.00	
Any Acute Neuropathy during Cycles 1-3		
Yes	3.65 (1.40 – 9.56)	0.008
No	1.00	
Weight, per additional kilogram	0.93 (0.89 – 0.97)	0.0006