

Neurological Toxicity in Metastatic Colorectal Cancer Patients Treated with Modified FOLFOX6 Plus Bevacizumab

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ABSTRACT: This study was conducted to investigate the toxicity and efficacy of modified FOLFOX6 plus bevacizumab in patients with metastatic colorectal cancer with particular regard to oxaliplatin-induced neuropathy. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 3.0). The evaluation was especially focused on grade 2 oxaliplatin-induced neuropathy. The estimated median treatment time to occurrence of grade 2 sensory neuropathy was 7.3 months. The estimated median cumulative dose to occurrence of grade 2 sensory neuropathy was 931 mg/m². This study clarified the treatment time from first dose as well as the cumulative dose of oxaliplatin leading to grade 2 neuropathy. It may be important to institute some clinical countermeasures when grade 2 neuropathy occurs so as to reduce the chance of progression to irreversible grade 3 neuropathy.

KEYWORDS: oxaliplatin, neuropathy, colorectal cancer, modified FOLFOX6

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Introduction

Colorectal cancer is one of the most frequent causes of cancer deaths worldwide.¹ Approximately 50–60% of patients diagnosed with colorectal cancer develop inoperable metastases.² Further, 40–50% of patients who undergo potentially curative surgery alone ultimately relapse and die of metastatic disease.³

Oxaliplatin is widely used in combination with 5-fluorouracil (5-FU) for the treatment of colorectal cancer in the adjuvant and metastatic setting.^{4,5} FOLFOX (consisting of fluorouracil, oxaliplatin, and folinic acid) plus bevacizumab is currently a standard first-line regimen for the management of patients with metastatic colorectal cancer.^{6,7}

Sensory neuropathy is one of the principal dose-limiting toxic effects of oxaliplatin. This oxaliplatin-induced neuropathy

can be acute or chronic.⁸ Acute oxaliplatin-induced neuropathy usually begins during the initial infusion or within one to two days following the administered dose and is often triggered by cold. By contrast, chronic oxaliplatin-induced neuropathy consists primarily of non-cold-related dysesthesias and paresthesias of the extremities. These symptoms are quite similar to those seen with cisplatin toxicity and generally persist between cycles.⁹

Oxaliplatin-induced neuropathy is the predominant reason for dose reduction, extension of the withdrawal period, and termination of therapy. Therefore, strategies to prevent or reverse this complication would enhance the efficacy and tolerability of regimens that contain this drug.

Two different strategies have been advocated to prevent oxaliplatin-induced neuropathy: a stop-and-go approach



(ie intermittent oxaliplatin dosing) and the concurrent use of neuromodulatory agents, including antidepressants, antiepileptics, or calcium and magnesium infusions. However, neither strategy is sufficiently effective.^{10,11}

Therefore, this study focused on oxaliplatin-induced neuropathy, especially grade 2 neuropathy, in order to improve the quality of medical practice in patients with metastatic colorectal cancer treated with modified FOLFOX6 plus bevacizumab.

Patients and Methods

Study design. This study was conducted as a prospective phase II study to investigate the toxicity and efficacy of modified FOLFOX6 plus bevacizumab for patients with metastatic colorectal cancer. The occurrence of oxaliplatin-induced neuropathy was specifically investigated. The study protocol was approved by the Institutional Review Board of Oita University, and written informed consent was obtained from patients before study entry.

Patient selection. The eligibility criteria for inclusion in the study were adenocarcinoma of the colon or rectum, unresectable metastases, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2, and age of 20–75 years. No prior chemotherapy or one prior chemotherapy regimen for advanced disease was eligible. Adjuvant chemotherapy was counted as one chemotherapy regimen if it had been completed less than six months before recurrence. All patients had to meet the following laboratory criteria within 14 days before registration: white blood cell count $\geq 3000 \times 10^3/\mu\text{L}$, platelet count $\geq 100 \times 10^3/\mu\text{L}$, hemoglobin level ≥ 8.0 g/dL, aspartate aminotransferase (AST) ≤ 100 IU/L, alanine aminotransferase (ALT) ≤ 100 IU/L, total bilirubin ≤ 1.5 mg/dL, serum creatinine ≤ 1.5 mg/dL, and no major electrocardiogram abnormalities.

Key exclusion criteria were as follows: surgery within 28 days before starting treatment or surgery anticipated during the study, planned radiotherapy for underlying disease, and history of malignancy other than metastatic colorectal cancer. Patients with uncontrolled hypertension, clinically significant cardiovascular disease, proteinuria ≥ 1 g/24 hours, hemorrhagic diathesis or coagulopathy, or serious non-healing wounds or ulcers were also excluded.

Treatment. Bevacizumab was administered as a 30- to 90-minute intravenous infusion before oxaliplatin at a dose of 5 mg/kg for first-line therapy or a dose of 10 mg/kg for second-line therapy on day 1 when given with modified FOLFOX6 (oxaliplatin 85 mg/m² IV with leucovorin 200 mg/m² IV over 2 hours on day 1 plus 5-FU 400 mg/m² IV bolus on day 1 and 2,400 mg/m² continuous infusion over 46 hours on days 1 and 2). Treatment was administered every two weeks until disease progression or unacceptable toxicity, or until the patient refused further treatment.

The next dose was delayed until recovery if the neutrophil count was less than $1.5 \times 10^3/\mu\text{L}$, if the platelet count

was less than $75 \times 10^3/\mu\text{L}$, or for significant persisting non-hematological toxicity. The dose of oxaliplatin was reduced to 65 mg/m² for patients who experienced persistent grade 2 neurotoxicity that did not resolve within two weeks. For patients with persistent grade 3 neurotoxicity, oxaliplatin was discontinued, but 5-FU/leucovorin and bevacizumab therapy was continued. In patients who recovered from grade 3 or 4 gastrointestinal toxicity, grade 4 neutropenia, or grade 3 or 4 thrombocytopenia, the oxaliplatin dose was reduced to 65 mg/m², and the 5-FU dose was reduced to 300 mg/m² IV bolus and a 2000 mg/m² continuous infusion.

Treatment was terminated when grade 4 non-hematological toxicity was observed, if the patient refused to continue, or when recovery from toxicity delayed the initiation of the next course by greater than three weeks from the planned schedule.

Bevacizumab dose reductions were not utilized. Instead, in cases of serious bevacizumab-related toxicity, bevacizumab was temporarily or permanently suspended.

Safety and efficacy. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 3.0). Toxicities were evaluated according to the most severe grade from each patient during the entire study interval. Detailed information regarding the course of severity of neuropathy was also collected.

Computed tomography (CT) scans of measurable lesions were assessed within four weeks before registration in this study as baseline findings; imaging was repeated every four cycles. Response Evaluation Criteria in Solid Tumors (RECIST)¹² were used to assess tumor response. Complete response was defined as complete disappearance of all clinically assessable disease for at least four weeks, and partial response was defined as a decrease of at least 30% of the sum of the longest diameters of measurable lesions for at least four weeks.

Statistical analysis. Incidence of grade 2 neuropathy, progression-free survival (PFS), and overall survival (OS) were calculated using the Kaplan–Meier method. The relationship between patient characteristics and grade 2 sensory neuropathy was evaluated with the chi-square test. A *P* value of <0.05 was considered to represent statistical significance. Grade 2 sensory neuropathy was defined as sensory alteration or paresthesia (including tingling) interfering with function but not interfering with activities of daily living (ADL). Grade 3 sensory neuropathy was defined as sensory alteration or paresthesia interfering with ADL according to NCI-CTCAE version 3.

All statistical analyses were carried out using StatView (Abacus Concepts, Berkeley, CA, USA).

Results

Patient characteristics. Between June 1, 2008, and August 31, 2010, 20 patients were enrolled. At the data cut-off date (April 25, 2011), the median duration of follow-up was 16.1 months. All patients were included in the toxicity



analysis. Baseline patient characteristics are shown in Table 1. The median age was 65 years (range, 46–74 years). Fourteen (70%) and six (30%) patients had an ECOG PS of 0 and 1, respectively. Eight (40%) patients received prior chemotherapy. Five (25%) patients were diabetic. Nine (45%) patients regularly consumed alcohol.

Anti-cancer drugs were administered for a median duration of eight cycles (range, 1–33 cycles). The reasons for discontinuation of study protocol were progressive disease ($n = 8$), bone marrow suppression ($n = 2$), venous thrombosis ($n = 2$), proteinuria ($n = 1$), bleeding ($n = 1$), and wound complication ($n = 1$).

Toxicity. Regimen toxicity is summarized in Table 2. Neutropenia, leukopenia, and anemia over grade 2 occurred in 70, 55, and 20% of patients, respectively. In terms of non-hematological toxicity, sensory neuropathy and hand–foot syndrome over grade 2 occurred in 45% (9/20) and 15% (3/20) of patients, respectively. Four patients who experienced grade 2 sensory neuropathy also developed grade 3 sensory neuropathy. Oxaliplatin dose reduction was required in 10 patients (50%); the major reason for dose reduction was sensory neuropathy ($n = 7$). Cessation of oxaliplatin because of sensory neuropathy was required in five patients.

Table 3 shows the relationship between the incidence of sensory neuropathy over grade 2 and potential predictive factors. Gender (male/female), age, ECOG PS (0/1), diabetes (with/without), and alcohol consumption (present/absent)

Table 2. Toxicity ($n = 20$).

ADVERSE EVENT	GRADE 1–4		GRADE 2–4	
	NO.	%	NO.	%
Neutropenia	17	85	14	70
Leukopenia	16	80	11	55
Anemia	9	45	4	20
Thrombocytopenia	14	70	2	10
Anorexia	14	70	2	10
Nausea	9	45	0	0
Stomatitis	11	55	1	5
Hand-foot syndrome	10	50	3	15
Sensory neuropathy	16	80	9	45
Allergic reaction	2	10	2	10
Hemorrhage	10	50	1	5
Hypertension	10	50	1	5
Thrombosis	3	15	2	10
Wound complication	2	10	2	10

at baseline were not significantly related to the incidence of grade 2 sensory neuropathy.

Kaplan–Meier curves were constructed to examine the incidence of grade 2 sensory neuropathy in relation to the time from the first dose. The incidence of grade 2 sensory neuropathy increased with the passage of time from the first

Table 1. Patient characteristics ($n = 20$).

Gender	
Male/Female	9/11
Age (years)	
Median (range)	65 (46–74)
ECOG performance status*	
0/1/2	14/6/0
Primary tumor site	
Colon/Rectum	12/8
No. of metastatic sites	
1/2/3	12/6/2
Resection of primary lesion	
Yes/No	15/5
Prior chemotherapy	
Yes/No	8/12
Prior radiotherapy	
Yes/No	3/17
Diabetes	
With/Without	5/15
Alcohol consumption	
Present/Absent	9/11

Note: *ECOG: Eastern Cooperative Oncology Group.

Table 3. Relationship between neurotoxicity and patient characteristics.

	SENSORY NEUROPATHY OVER GRADE 2		P VALUE
	YES	NO	
	n = 9	n = 11	
Gender			
Male	5	4	0.3907
Female	4	7	
Age (years)			
<65	5	5	0.6531
≥65	4	6	
ECOG performance status			
0	6	8	0.7686
1	3	3	
Diabetes			
With	3	2	0.4363
Without	6	9	
Alcohol consumption			
Present	6	3	0.0781
Absent	3	8	

Note: $P < 0.05$ (χ^2 test with Yates' correction).

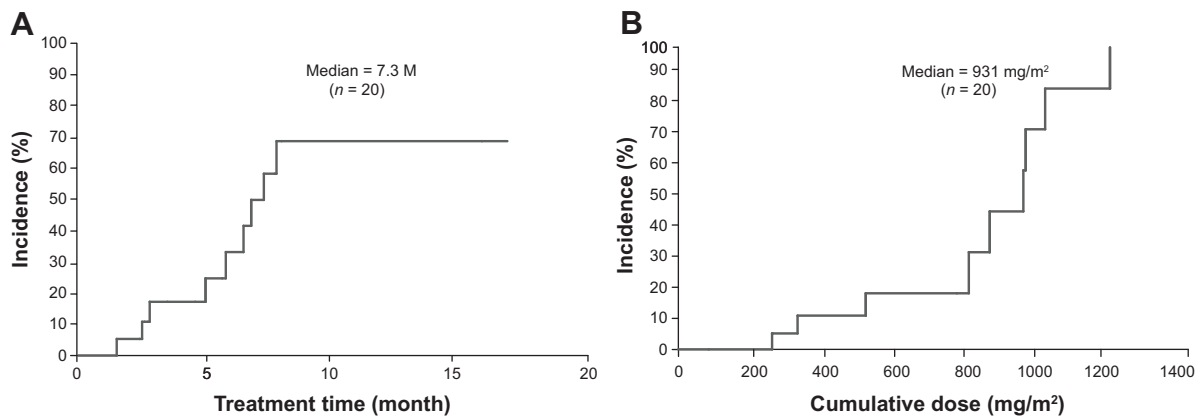


Figure 1. Relationship between the incidence of grade 2 oxaliplatin-induced neuropathy and time from first dose (A) or cumulative dose of oxaliplatin (B).

dose (Fig. 1A). The median time from the first dose of oxaliplatin to onset of grade 2 sensory neuropathy was 7.3 months, which was equivalent to approximately 11 cycles of treatment. The median time to progression from grade 2 neuropathy to grade 3 neuropathy was 35 days.

Figure 1B shows the incidence of sensory neuropathy in relation to the cumulative dose of oxaliplatin. The incidence of grade 2 sensory neuropathy increased along with an increase in the cumulative dose of oxaliplatin. The median oxaliplatin dose at which grade 2 sensory neuropathy occurred was 931 mg/m².

Efficacy. The objective response rate (ORR) was 31% (5/16), and the disease control rate (complete response + partial response + stable disease) was 100% (16/16). The median time to treatment failure (TTF) and PFS were 5.8 and 8.7 months, respectively. The median survival time was 19.7 months. None of the patients had undergone surgery with curative intent.

Discussion

This prospective trial investigated the toxicity of modified FOLFOX6 with bevacizumab in patients with metastatic advanced colorectal cancer with particular regard to oxaliplatin-induced neuropathy.

Common side effects of oxaliplatin include cytopenias, peripheral neuropathy, diarrhea, and nausea.¹³ Oxaliplatin-induced neurotoxicity is a recognized dose-limiting complication,¹⁴ and the incidence of oxaliplatin-induced neuropathy ranges from 65 to 100%.¹⁵ Grade 2 or worse neuropathy occurs in approximately 40–50% of patients receiving oxaliplatin, with grade 3 neuropathy occurring in 10–20% of patients.^{4,5,16} Most cases of grade 2 or worse neuropathy are chronic in nature. Severe (grade 3) cases of oxaliplatin-induced neuropathy occur in up to 30% of patients treated with cumulative doses ranging from 765 to 1020 mg/m.^{2,17–19}

There are several rating systems for neuropathy, including the total neuropathy score (TNS), the ECOG toxicity criteria, the oxaliplatin-specific scale, and criteria from individual studies or the World Health Organization.²⁰ These tools might

have provided more detailed information regarding symptomatology, and their use within the present protocol might have markedly improved the findings of this study. However, most clinical trials studying oxaliplatin use the NCI-CTCAE,⁸ therefore, we conducted evaluation of sensory neuropathy using the NCI-CTCAE.

Grade 2 sensory neuropathy was defined as sensory alteration or paresthesia (including tingling) interfering with function but not interfering with ADL, whereas grade 3 sensory neuropathy was defined as sensory alteration or paresthesia interfering with ADL, according to NCI-CTCAE version 3. Almost all previous studies that investigated oxaliplatin-induced neuropathy focused on grade 3 toxicity, whereas the current study investigated grade 2 toxicity. An analysis of grade 2 neurotoxicity is important because neuropathy \geq grade 3 can be irreversible and because the reduction or temporary cessation of oxaliplatin in response to grade 2 neuropathy might reduce the risk of progression to potentially irreversible neuropathy.

In the current study, 45% of patients ($n = 9$) had grade 2 sensory neuropathy and 20% of patients ($n = 4$) developed grade 3 neuropathy. Although few reports have described the time to occurrence of grade 2 neuropathy, the present study clarified that its median time was 7.3 months. One study by Grothey et al reported the time from first dose without grade 2 neuropathy, but the median time to development of neuropathy had not yet been reached in their patient population.¹¹ A study by de Gramont et al suggested that the estimated incidence of grade 2 neuropathy for patients exposed to oxaliplatin was 50% after 10 cycles,⁵ which is similar to observations from the present study (11 cycles).

In our study, the median cumulative dose of oxaliplatin at which grade 2 neuropathy occurred was 931 mg/m², which is a dose that is almost equal to that reported for grade 3 neuropathy in a previous study. This means that each treatment time and cumulative dose of oxaliplatin do not greatly differ between grades 2 and 3.

One of the aims of this study was to evaluate whether pre-treatment clinical parameters (eg age, gender, diabetes,



alcohol consumption) may serve as predictive factors for the development of oxaliplatin-induced neuropathy. However, these relationships could not be evaluated by multivariate analysis, because the number of patients was too small. Of note, there was a non-statistically significant trend toward a correlation between alcohol consumption and neuropathy over grade 2, which is consistent with the well-documented notion that chronic alcohol consumption can affect the peripheral nervous system.²¹

The median time to progression from grade 2 neuropathy to grade 3 neuropathy was 35 days, which is thought to be relatively short, and the amount of oxaliplatin required for progression from grade 2 neuropathy to grade 3 neuropathy was relatively small. This observation suggests that it may be important to reduce the dose or to stop administration of oxaliplatin when grade 2 neuropathy occurs so as to reduce the chance of progression to irreversible grade 3 neuropathy.

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Author Contributions

Conceived and designed the experiments, analyzed the data, wrote the first draft of the manuscript, and contributed to the writing of the manuscript: SO. Agreed with manuscript results and conclusions: SO, KW, RM, YH, KN, HS, KS. Jointly developed the structure and arguments for the study: SO, KW, RM, YH, KN, HS, KS. Made critical revisions and approved the final version: KS. All authors reviewed and approved the final manuscript.

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