Preventive Effect of Traditional Japanese Medicine on Neurotoxicity of FOLFOX for Metastatic Colorectal Cancer: A Multicenter Retrospective Study

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Abstract. *Background: A combination of 5-fluorouracil/folinic acid plus oxaliplatin (FOLFOX) is a standard regimen for the chemotherapy of metastatic colorectal cancer. The major dose-limiting toxic effect of oxaliplatin is neurotoxicity. The aim of this study was to evaluate the preventive effects of traditional Japanese medicines, goshajinkigan and shakuyakukanzoto on oxaliplatin-induced neurotoxicity with FOLFOX. Patients and Methods: Between July 2006 and November 2008, a total of 44 patients with metastatic colorectal cancer received modified FOLFOX6 or FOLFOX4, as first-line chemotherapy at three institutions. They concurrently received either goshajinkigan (group A, n=20) or shakuyakukanzoto (group B, n=24) for neurotoxicity reduction. Results: The median number of treatment cycles and the median cumulative dose of oxaliplatin were 12 cycles (range, 4-19) and 898 mg/m^2 (range, 340-1255) in group A and 10.5 cycles (range, 6-20) and 845 mg/m^2 (range, 510-1480) in group B. Eighteen patients in group A and 24 in group B received oxaliplatin in a cumulative dose exceeding 500 mg/m^2. At a dose of 500 mg/m^2 oxaliplatin, grade 1-2 toxicity occurred in 10 patients of group A and in 7 of group B, but there was no grade 3 or higher toxicity in either group. The response rate of the 38 patients with measurable lesions was 50.0% (9/18) in group A and 65% (13/20) in group B. Conclusion: The administration of traditional Japanese medicine may reduce oxalipatin-induced neurotoxicity without negatively affecting tumor response in patients with colorectal cancer who undergo FOLFOX therapy.*

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5-Fluorouracil/folinic acid plus oxaliplatin (FOLFOX) is used as standard chemotherapy for metastatic colorectal cancer. Chronic neurotoxicity is a dose-limiting toxic effect of oxaliplatin and is the major reason for discontinuation of FOLFOX, apart from tumor progression (1). Severe neurotoxicity with functional impairment occurred in 15% to 20% of patients who received oxaliplatin in a cumulative dose of 750 to 850 mg/m^2 in phase III trials (1, 2). Although several neuroprotective agents, such as calcium-magnesium and anticonvulsants, have been used to suppress oxaliplatin-induced neurotoxicity in clinical trials (3-6), an effective and safe treatment for neurotoxicity remains to be established.

Goshajinkigan (Tsumura & Co. Ltd., Tokyo, Japan), a traditional Japanese medicine containing ten herbal components (Table I), is considered to relieve from symptoms such as numbness and cold sensation in patients with diabetic neuropathy (7). The three-dimensional high performance liquid chromatography (HPLC) profile of goshajinkigan is shown in Figure 1. Recent studies have reported that goshajinkigan reduces the neurotoxicity of oxaliplatin, without negatively affecting response in patients with cancer who undergo FOLFOX therapy (8, 9). Shakuyakukanzoto (Tsumura & Co. Ltd., Tokyo, Japan) is an extract of a mixture of glycyrrhiza and peony root (Table I). This traditional Japanese medicine has been reported to effectively reduce muscle pain, muscle spasms, joint pain, and numbness (10-12). The three-dimensional HPLC profile of shakuyakukanzoto is shown in Figure 2.

Shakuyakukanzoto has also been shown to be effective against paclitaxel-induced peripheral neuropathy (13). The aim of the present study was to evaluate the preventive effects of goshajinkigan and shakuyakukanzoto on oxaliplatin-induced neurotoxicity.

Patients and Methods

A total of 44 patients with metastatic colorectal cancer received modified FOLFOX6 or FOLFOX4 as first-line chemotherapy between July 2006 and November 2008 at three institutions. They concurrently received either goshajinkigan (group A, n=20) or shakuyakukanzoto (group B, n=24) to reduce neurotoxicity. Goshajinkigan (7.5 g/day) and shakuyakukanzoto (7.5 g/day) were administered orally, in three divided doses, before or between meals every day during FOLFOX therapy. Bevacizumab (BV) was added to FOLFOX for two patients in group A and for 15 patients in group B. The responses of metastatic lesions were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (14). Toxic effects other than neurotoxicity were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Neurotoxicity was assessed according to the Neurotoxicity Criteria of DEBIOPHARM (DEB-NTC) (15) as follows: grade 1, paresthesia or dysesthesia lasting up to 7 days; grade 2, paresthesia or dysesthesia lasting more than 7 days; and grade 3, persistent functional impairment.

Statistical analysis. The occurrence of peripheral neurotoxicity was assessed with the Kaplan–Meier method. If neurotoxicity had occurred at the time of the last recording, data were not used. The two groups were compared with the use of the chi-square test, Student's *t*-test, and Fisher's exact test. All statistical analyses were performed using the JMP, version 9, software (SAS Institute, Cary, NC, USA).

Results

Patients' characteristics. The baseline characteristics of each group are shown in Table II. The median age was 66.5 years (range=48-79) in group A and 60 years (range=43-78) in group B. Good performance status of 0 to 1 was confirmed in 18 patients in group A and 24 patients in group B. Age, gender, performance status, site of primary tumor, and prior adjuvant chemotherapy did not differ significantly between group A and group B.

Treatment profile of FOLFOX therapy. The details of FOLFOX therapy are shown in Table III. Most patients in each group underwent modified FOLFOX6 therapy, although two in group A underwent FOLFOX4 therapy. The median number of treatment cycles and median cumulative oxaliplatin dose were similar in the two groups and were, 12 cycles (range=4-19) and 898 mg/m^2 (range=340-1255) in group A and 10.5 cycles (range=6-20) and 845 mg/m^2 (range=510-1480) in group B. Eighteen patients in group A and 24 in group B received oxaliplatin in a cumulative dose exceeding 500 mg/m^2. Bevacizumab was added to FOLFOX in two patients in group A and 15 patients in group B. There were no significant differences between the two groups except for the use of bevacizumab. All patients were treated on an outpatient basis during most of the treatment period.

Chronic neurotoxicity. Following Kaplan–Meier analysis, in group A, 10 patients had grade 1-2 neurotoxicity, and none had grade 3 neurotoxicity at a total oxaliplatin dose of 500 mg/m^2. In group B, seven patients had grade 1-2 neurotoxicity and

Table I. *Components of goshajinkigan and shakuyakukanzoto*.

Goshajinkigan	
7.5 g of goshajinkigan contains 4.5 g of a dried extract of the following mixed herbal components:	
Rehmannia root	5.0 g
Achyranthes root	3.0 g
Cornus fruit	3.0 g
Dioscorea rhizome	3.0 g
Plantago seed	3.0 g
Alisma rhizome	3.0 g
Poria sclerotium	3.0 g
Moutan bark	3.0 g
Cinnamon bark	1.0 g
Processed aconite root	1.0 g
Shakuyakukanzoto	
7.5 g of shakuyakukanzoto contains 2.5 g of a dried extract of the following mixed herbal components:	
Glycyrrhiza	6.0 g
Peony root	6.0 g

Table II. *Patients' characteristics*.

	Group A (n=20)	Group B (n=24)	*p*-Value
Age (years)			0.23
Median (range)	66.5 (48-79)	60 (45-78)	
Gender			0.28
Male/female	14/6	13/11	
ECOG performance status			0.20
0-1/2	18/2	24/0	
Site of primary tumor			0.24
Colon/rectum	15/5	14/10	
No. of metastatic sites			0.26
1/≥2	10/10	16/8	
Prior adjuvant chemotherapy			0.79
Yes/no	2/18	3/21	

ECOG, Eastern Cooperative Oncology Group.

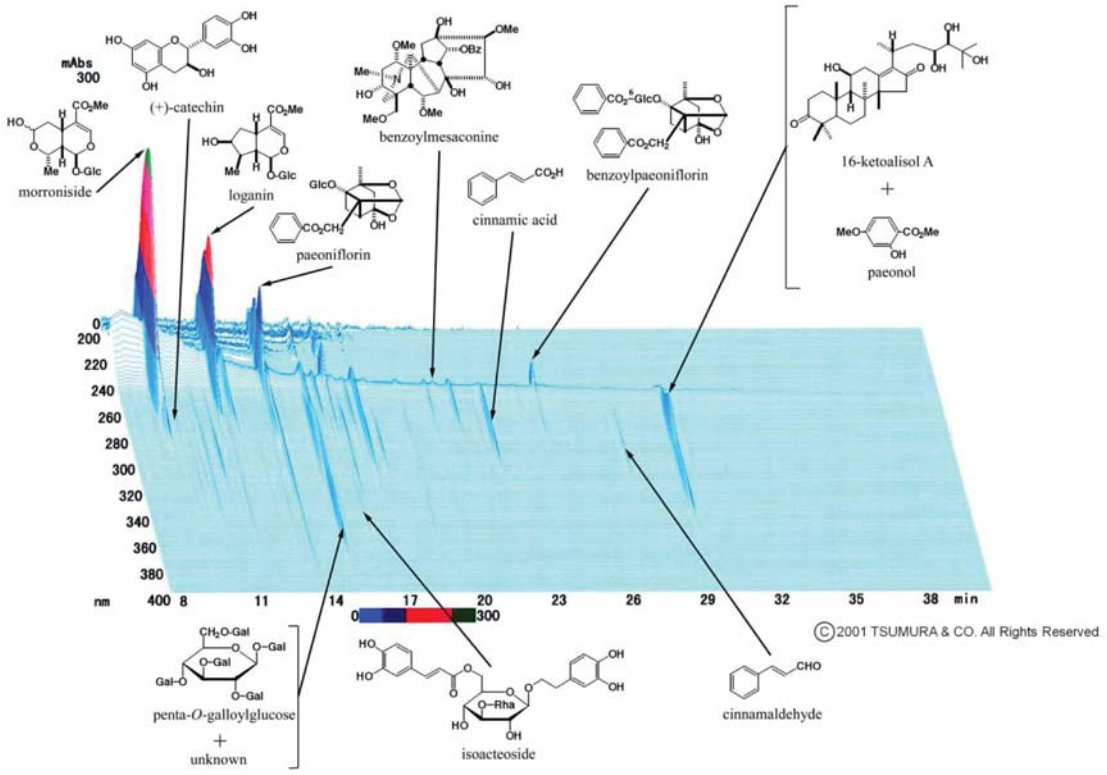

Figure 1. *Three-dimensional high performance liquid chromatography (HPLC) profile of goshajinkigan.*

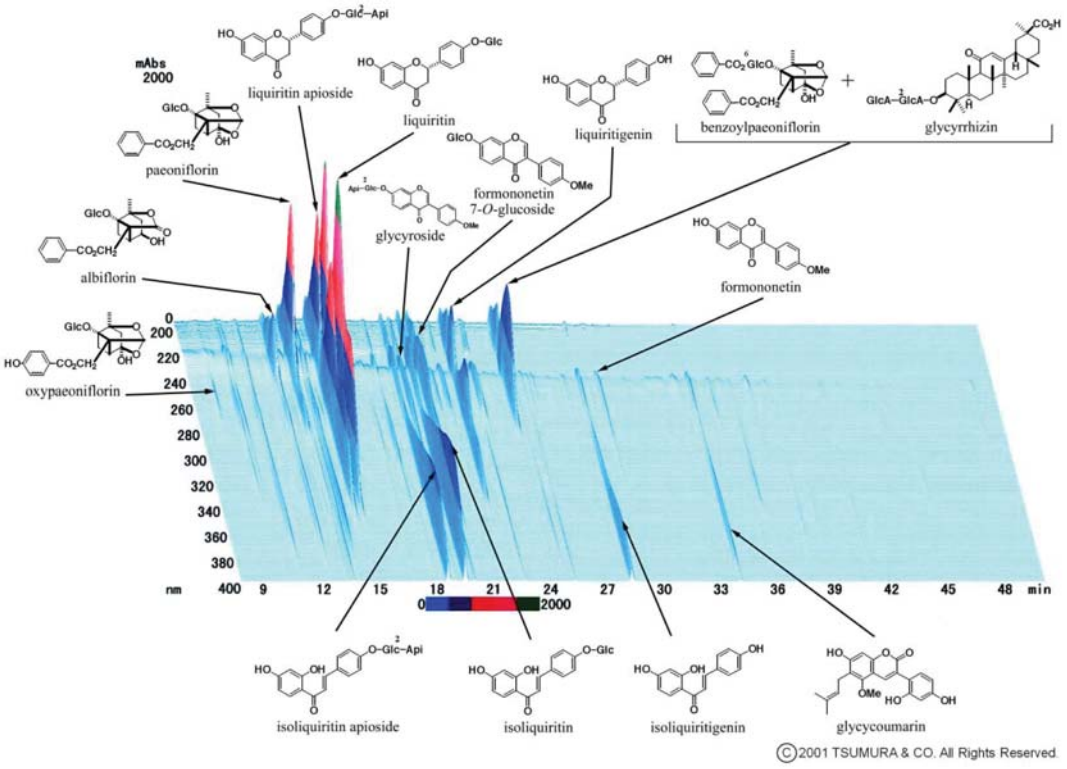

Figure 2. *Three-dimensional high performance liquid chromatography (HPLC) profile of shakuyakukanzoto.*

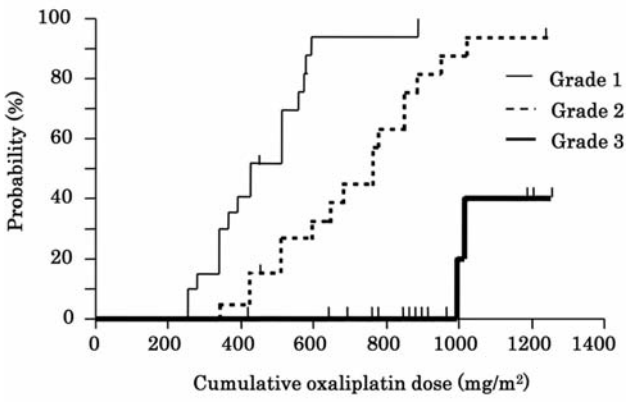

Figure 3. *Kaplan–Meier analysis of neurotoxicity in group A. At a dose of 500 mg/m², grade 1-2 neurotoxicity was observed in 10/18 patients.*

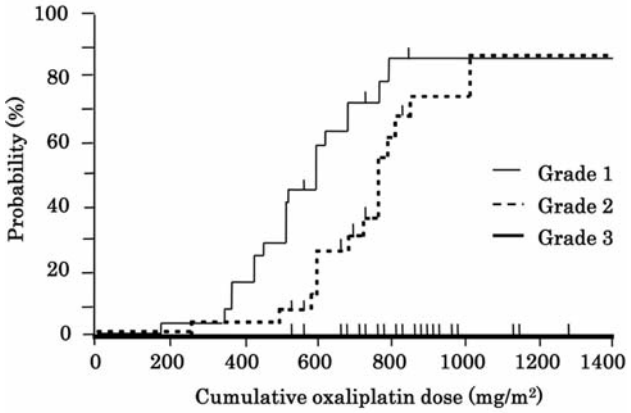

Figure 4. *Kaplan–Meier analysis of neurotoxicity in group B. At a dose of 500 mg/m², grade 1-2 neurotoxicity was observed in 7/24 patients.*

Table III. *Treatment profile of FOLFOX therapy.*

	Group A (n=20)	Group B (n=24)	*p*-Value
Treatment type			0.071
FOLFOX4	2	0	
mFOLFOX6	18	24	
No. of cycles of FOLFOX			0.23
Median (range)	12 (4-19)	10.5 (6-20)	
Cumulative dose of oxaliplatin (mg/m²)			0.073
Median (range)	898 (340-1255)	845 (510-1480)	
No. of patients who received oxaliplatin ≥500 mg/m²			0.071
Yes/no	18/2	24/0	
Use of bevacizumab			<0.0001
Yes/no	2/18	15/9	

Table IV. *Toxicity profiles.*

	Group A (N=20)		Group B (N=24)	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Leukopenia	18	2	20	1
Neutropenia	16	8	19	7
Anemia	14	1	17	1
Thrombocytopenia	17	2	20	0
Nausea	15	0	21	0
Anorexia	17	0	22	0
Diarrhea	11	0	7	0
Fatigue	17	0	21	0
Chronic Neuropathy	18	2	20	1
Hypersensivity	2	0	3	0
Hypokalemia	4	0	7	1

none had grade 3 neurotoxicity at a total oxaliplatin dose of 500 mg/m² (Figures 3 and 4). Finally, grade 3 neurotoxicity developed in two patients of group A and in one patient of group B.

Toxicity. Toxicity was assessed in all patients. The highest-grade toxic effects in each group are shown in Table IV. The most common grade 3/4 toxicities were similar in both groups, including leukopenia, neutropenia, and thrombocytopenia. Of note, grade 3 hypokalemia (potassium level, 2.6 mEq/l) occurred in one patient (4%) in group B.

Tumor response. The overall responses are summarized in Table V. The response rate (*i.e.* complete and partial responses) of the 38 patients with measurable lesions was 9/18 (50.0%; 95% confidence interval (CI): 38.5 to 61.5%) in group A and 13/20 (65%, 95% CI: 44.1 to 85.9%) in group B.

Table V. *Response rates for the treatment arms.*

Response	Group A	Group B
No. of patients assessible	18	20
Complete response	0	1
Partial response	9	12
Stable disease	8	7
Progressive disease	1	0
Response rate	50.0%	65.0%
95% Confidence interval	38.5 to 61.5	44.1 to 85.9

Discussion

In the present study, we investigated the prophylactic effectiveness of goshajinkigan and shakuyakukanzoto for oxaliplatin-induced neurotoxicity in patients with

metastatic colorectal cancer. Although the mechanisms of these two medicines remain to be fully elucidated, goshajinkigan has been reported to have antinociceptive effects caused by increased nitric oxide production and induction of dynorphin release in the spinal cord (16). The antinociceptive effects of shakuyakukanzoto have been attributed to the activation of spinal-descending noradrenergic neurons (17).

Gamelin *et al*. retrospectively analyzed the preventive effects of calcium and magnesium treatment against oxaliplatin-induced neurotoxicity in patients with advanced colorectal cancer. At a cumulative dose of 500-520 mg/m^2 of oxaliplatin, neurotoxicity occurred in 86% of the untreated group and 51% of the calcium-magnesium treatment group (18). In our study, the incidence of all-grade neurotoxicity was 10/18 of group A and 7/24 in group B, at a cumulative oxaliplatin dose of 500 mg/m^2. There was no grade 3 or higher neurotoxicity in either group at this dose-level. In previous randomized phase III studies, the incidence of severe neurotoxicity was 15% to 20% in patients who received FOLFOX therapy (1, 2). In the present study, the overall incidence of grade 3 neurotoxicity was 2/20 in group A and 1/24 in group B during FOLFOX therapy. Thus, our results suggest that goshajinkigan and shakuyakukanzoto may reduce oxalipatin-induced neurotoxicity and that shakuyakukanzoto may be more effective for the prevention of neurotoxicity associated with FOLFOX.

As for other toxic effects, the findings in our study were similar to those of previous randomized phase III studies, except for the occurrence of grade 3 hypokalemia in group B. Shakuyakukanzoto has been shown to potentially cause hypokalemia due to pseudoaldosteronism (19, 20). Although one patient had grade 3 hypokalemia in group B, this adverse effect was resolved after reducing the daily dose of shakuyakukanzoto from 7.5 g/day to 5.0 g/day.

Several studies reported that goshajinkigan had no impact on tumor response to FOLFOX therapy (8, 9). In our study, the response rate was 9/18 in group A and 13/20 in group B. Goshajinkigan and shakuyakukanzoto seemed not to negatively affect response rates as compared with those previously reported for FOLFOX therapy (1, 2).

Our study had several important limitations. It was a retrospective, non-randomized study of a small number of patients without the use of a control arm. Selection bias may have also potentially affected our results. Our findings should thus be tested in prospective clinical trials.

In conclusion, the traditional Japanese medicines goshajinkigan and shakuyakukanzoto may reduce oxalipatin-induced neurotoxicity without a negative impact on tumor response in patients with metastatic colorectal cancer who receive FOLFOX therapy. Our results suggest that further evaluation of traditional Japanese medicines are warranted in patients administered with FOLFOX therapy.

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