

Safety and continuity of second- and third-line therapy with paclitaxel or irinotecan for advanced and recurrent gastric cancer

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Abstract. In the treatment of advanced or recurrent gastric cancer, the prolongation of survival depends on the use of second-line therapy, with paclitaxel (PTX) or irinotecan (CPT-11) as the key agents. The present study aimed to retrospectively investigate the safety and continuity of weekly PTX and CPT-11 monotherapy as second- or third-line treatment for advanced or recurrent gastric cancer. A total of 62 patients who had received PTX or CPT-11 for gastric cancer at the Ogaki Municipal Hospital (Ogaki, Japan) were retrospectively reviewed. Of the 47 patients who received PTX as second-line therapy, 13 (27.7%) received third-line therapy with CPT-11. Second-line PTX and third-line CPT-11 were discontinued due to progressive disease (PD) in 27 and 7 cases, respectively, and deterioration in the performance status (PS) in 20 and 4 cases, respectively. Only 1 case of discontinuation due to adverse events (AEs) was reported for third-line CPT-11. Furthermore, of the 15 patients who received CPT-11 as second-line treatment, 11 (73.3%) then received PTX as third-line treatment. Second-line CPT-11 and third-line PTX were discontinued due to PD in 9 and 6 cases, respectively, and deterioration in the PS in 4 and 5 cases, respectively, whereas there was only 1 case of discontinuation due to AEs for second-line CPT-11. Severe AEs for PTX and CPT-11 were infrequent; however, the frequency of diarrhea was high when PTX was administered as third-line therapy (63.6%), whereas the frequency of malaise was high when CPT-11 was administered as second- (73.3%) and third-line (76.9%) therapy. In conclusion, severe AEs due to PTX and CPT-11 as second- and third-line treatment for advanced or recurrent gastric cancer are infrequent and patients are generally able to continue treatment. However, the

possibility of diarrhea with third-line PTX and malaise with second- and third-line CPT-11 treatment should be considered when planning chemotherapy.

Introduction

Tegafur-gimeracil-oteracil potassium (S-1) plus cisplatin is currently recommended as the standard first-line chemotherapy for advanced or recurrent gastric cancer in Japan, according to the results of the Japan Clinical Oncology Group 9912 (1) and those of the S-1 plus cisplatin vs. S-1 alone in randomized clinical trials for the first-line treatment of advanced gastric cancer (SPIRITS) trial (2). As regards second-line treatment, weekly paclitaxel (PTX) (3-9), irinotecan (CPT-11) monotherapy (10-15), S-1 plus PTX (16) and S-1 plus CPT-11 (17,18) are used in daily practice. The prolongation of survival depends on the treatment following first-line therapy, with PTX and CPT-11 used as the key agents (19-21).

Akasaka *et al* (22) reported that tolerability to S-1 plus CPT-11 for advanced or recurrent gastric cancer differs between cases with a performance status (PS) of 2 and those with a PS of 0-1. In addition, we previously reported a high frequency of adverse events (AEs) associated with S-1 plus cisplatin treatment or S-1 monotherapy in patients with a poor nutritional status (23,24) and observed that a PS of ≥ 1 and serum albumin levels (Alb) of <3.5 g/dl were risk factors for discontinuation of treatment due to AEs. Therefore, the tolerance to CPT-11 and PTX may decrease with deterioration of the patient's condition. In particular, we hypothesized that tolerance to chemotherapy decreases with the transition from second- to third-line therapy. However, the frequency of AEs and treatment continuity associated with second- and third-line chemotherapy with PTX or CPT-11 have not been sufficiently investigated. Therefore, this study aimed to retrospectively investigate the safety and continuity of PTX and CPT-11 as second- and third-line treatment for advanced or recurrent gastric cancer.

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Subjects and methods

Patients and treatment. Between April, 2006 and March, 2013, 139 patients received S-1 plus cisplatin therapy as

first-line treatment for advanced or recurrent gastric cancer at the Ogaki Municipal Hospital (Ogaki, Japan). In 62 of these cases, the patients later received CPT-11 or PTX as second- and third-line therapy. Data on treatment dose, PS, Alb, reasons for treatment discontinuation and frequency of AEs were retrospectively collected. The treatment dose was calculated as the ratio of the actual to the standard dose. All the data, such as treatment dose, PS and treatment duration, are presented as median value and range. Data on AEs, treatment dose, PS and reasons for discontinuation of chemotherapy were extracted from electronic charts and records of medication management and instructions completed by physicians. The severity of AEs was classified according to the Common Terminology Criteria for Adverse Events, version 4.0.

This study was approved by the Institutional Review Board of the Ogaki Municipal Hospital.

Doses and routes of PTX and CPT-11. PTX was administered intravenously (i.v.) at a starting dose of 80 mg/m² over 1 h weekly on days 1, 8 and 15 over a 4-week period. Irinotecan was administered i.v. at a starting dose of 150 mg/m² over 1.5 h weekly on day 1 of each 2-week period.

Statistical analysis. The Mann-Whitney U test was used for comparisons between two groups and comparisons among multiple groups were performed with one-factor analysis of variance. In all significance tests, $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient characteristics. The patient characteristics are summarized in Table I. For the patients who received second-line PTX and CPT-11, the median age was 65 years (range, 49-79 years) and 66 years (range, 42-78 years), respectively; unresectable tumors were identified in 35 and 4 cases and recurrent disease in 12 and 11 cases ($P = 0.0016$), respectively. Peritoneal metastasis was identified in 26 and 2 patients who received second-line PTX and CPT-11, with a PS of 1 (range, 0-2) and 0 (range, 0-2), respectively. Furthermore, the patients who received second-line PTX and CPT-11 had an Alb level of 3.7 g/dl (range, 2.0-4.5 g/dl) and 4.1 g/dl (range, 2.4-4.9 g/dl), respectively.

Reasons for discontinuation and AEs with second- and third-line therapy in patients who received second-line PTX. The reasons for treatment discontinuation and the AEs with second- and third-line treatment in patients who received second-line PTX are summarized in Tables II and III, respectively.

Rate of transition to third-line treatment. Of the 47 patients who received second-line PTX, 13 (27.7%) later received third-line treatment.

Reasons for discontinuation. Second-line PTX or third-line CPT-11 were discontinued due to progressive disease (PD) in 27 and 7 cases, respectively and deterioration in the PS in 20 and 4 cases, respectively. Discontinuation due to AEs was reported in only 1 case of third-line CPT-11. That patient requested withdrawal of the treatment due to nausea.

Table I. Patient characteristics.

Characteristics	Second-line PTX ^a (n=47)	Second-line CPT-11 ^b (n=15)
Age, years		
Median (range)	65 (49-79)	66 (42-78)
Gender		
Female	12	2
Male	35	13
ECOG performance status		
0	16	9
1	28	6
2	3	0
Disease status		
Unresectable	35	4
Recurrent	12	11
Metastatic site		
Lymph nodes	16	7
Liver	17	11
Lung	2	0
Bone	1	0
Peritoneum	26	2
Spleen	2	1
Treatment cycles (first-line)		
1-2	7	2
3-4	11	5
5-6	13	3
7-8	7	3
≥9	9	2
Others (range)		
Performance status	1 (0-2)	0 (0-2)
Serum albumin level, g/dl	3.7 (2.0-4.5)	4.1 (2.4-4.9)

^aPatients who received paclitaxel as second-line treatment. ^bPatients who received irinotecan as second-line treatment. PTX, paclitaxel; CPT-11, irinotecan; ECOG, Eastern Cooperative Oncology Group.

Duration of therapy and treatment dose. The duration of therapy was 120 days (range, 7-1,119 days) and 182 days (range, 28-497 days) and the median treatment dose was 100% (range, 60-100%) and 100% (range, 80-100%) for patients who received second-line PTX and third-line CPT-11, respectively.

PS and serum Alb level. Patients who received second-line PTX and then third-line treatment had a PS of 1 (range, 0-1) and 1 (range, 0-2) and Alb levels of 3.7 g/dl (range, 3.1-4.3 g/dl) and 3.5 g/dl (range, 2.3-4.3 g/dl), respectively, prior to the administration of second- and third-line treatment.

AEs. The AEs observed following second-line PTX included neutropenia (59.6%), leukopenia (59.6%), oligochromemia (76.6%), sensory neuropathy (76.6%) and constipation (68.1%). The AEs observed with third-line CPT-11 included malaise (76.9%) and oligochromemia (76.9%).

Table II. Reasons for discontinuation with second- and third-line therapy in patients who received second-line PTX.

A, Discontinuation following second-line CPT-11		
Variables	Second-line PTX ^a (n=47)	Third-line CPT-11 ^b (n=13)
Transition rate, % (n/total)	27.7 (13/47)	
Reason for discontinuation		
Adverse events	0	1
Progressive disease	27	7
Decrease in PS	20	4
Other	0	1
Continuity period, days		
Median (range)	120 (7-1,119)	182 (28-497)
Treatment dose, %		
Median (range)	100 (60-100)	100 (80-100)

B, PS and serum Alb levels

PS and serum Alb by treatment transition	At the start of second-line PTX	At the end of second-line PTX	At the end of third-line CPT-11	P-values
PS, value (range)				
Patients who transitioned to third-line treatment	1 (0-1)	1 (0-2)	2 (0-3)	0.0002
Patients who stopped at second-line treatment	1 (0-2)	3 (1-3)	-	<0.0001
Serum Alb level, g/dl (range)				
Patients who transitioned to third-line treatment	3.7 (3.1-4.3)	3.5 (2.3-4.3)	2.8 (2.1-3.5)	0.0014
Patients who stopped at second-line treatment	3.8 (2.0-4.5)	2.9 (2.1-4.1)	-	0.0026

^aPatients who received paclitaxel as second-line treatment; ^bPatients who received irinotecan as third-line treatment; PTX, paclitaxel; CPT-11, irinotecan; PS, performance status; Alb, albumin.

Reasons for discontinuation and AEs with second- and third-line therapy in patients who received second-line CPT-11. The reasons for discontinuation and the AEs associated with second- and third-line therapy in patients who received second-line CPT-11 are summarized in Tables IV and V, respectively.

Rate of transition to third-line treatment. Of the 15 patients who received second-line CPT-11, 11 (73.3%) then received third-line treatment.

Reasons for discontinuation. Second-line CPT-11 or third-line PTX was discontinued due to PD in 9 and 6 cases, respectively, and deterioration in the PS in 4 and 5 cases, respectively. Discontinuation due to AEs was reported in only 1 case following second-line CPT-11. That patient experienced anorexia and malaise.

Duration of therapy and treatment dose. The duration of therapy was 138 days (range, 28-566 days) and 110 days (range, 17-350 days) and the treatment dose was 100% (range, 80-100%) and 100% (range, 100-100%) for patients who

received second-line CPT-11 and third-line PTX, respectively.

PS and serum Alb level. The patients who received second-line CPT-11 and then third-line treatment had a PS of 0 (range, 0-1) and 0 (range, 0-2) and Alb levels of 4.2 g/dl (range, 3.2-4.9 g/dl) and 4.1 g/dl (range, 3.2-4.8 g/dl), respectively, prior to second- and third-line treatment.

AEs. The AEs observed with second-line CPT-11 were mainly malaise (73.3%) and nausea (60.0%), whereas diarrhea (63.6%) and sensory neuropathy (63.6%) were commonly observed with third-line PTX (Table V).

Incidence of neutropenia with second- and third-line treatment in patients who transitioned to third-line treatment. A total of 15 patients experienced neutropenia with second-line treatment (PTX or CPT-11) and 5 patients experienced neutropenia with third-line treatment (PTX or CPT-11); the difference was found to be statistically significant (P=0.0039; Table VI).

Table III. Adverse events with second- and third-line therapy in patients who received second-line PTX.

Adverse events	Second-line PTX ^a (n=47)		Third-line CPT-11 ^b (n=13)	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Leucopenia	28 (59.6)	2 (4.3)	2 (15.4)	0 (0.0)
Neutropenia	28 (59.6)	7 (14.9)	2 (15.4)	2 (15.4)
Oligochromemia	36 (76.6)	2 (4.3)	10 (76.9)	1 (7.7)
Thrombocytopenia	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)
AST/ALT increase	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Febrile neutropenia	3 (6.4)	3 (6.4)	1 (7.7)	1 (7.7)
Nausea	9 (19.1)	0 (0.0)	5 (38.5)	0 (0.0)
Vomiting	5 (10.6)	0 (0.0)	4 (30.8)	0 (0.0)
Malaise	27 (57.4)	0 (0.0)	10 (76.9)	1 (7.7)
Diarrhea	4 (8.5)	0 (0.0)	7 (53.8)	0 (0.0)
Anorexia	23 (48.9)	1 (2.1)	8 (61.5)	1 (7.7)
Stomatitis	4 (8.5)	0 (0.0)	1 (7.7)	0 (0.0)
Sensory neuropathy	36 (76.6)	1 (2.1)	8 (61.5)	0 (0.0)
Constipation	32 (68.1)	0 (0.0)	9 (69.2)	0 (0.0)
Taste alteration	7 (14.9)	0 (0.0)	1 (7.7)	0 (0.0)
Infusion site extravasation	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Hot flushes	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	2 (4.3)	0 (0.0)	5 (38.5)	0 (0.0)
Nail discoloration	4 (8.5)	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (2.1)	0 (0.0)	0 (0.0)	0 (0.0)

^aPatients who received paclitaxel as second-line treatment; ^bPatients who received irinotecan as third-line treatment; PTX, paclitaxel; CPT-11, irinotecan; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Discussion

CPT-11 and PTX as second- and third-line chemotherapies are currently the most effective treatments for advanced or recurrent gastric cancer (19); however, the tolerability to treatment may be reduced, depending on the condition of the patients (22-24). The findings of 4,007 comparative phase III trials of PTX and CPT-11 as second-line treatment for advanced gastric cancer, conducted by the West Japan Oncology Group (WJOG; WJOG4007) were reported at the American Society of Clinical Oncology meeting in 2012 (25). Ueda *et al* (25) reported that the rate of transition from second- to third-line treatment was higher with second-line CPT-11 (90%) compared to that with second-line PTX (72%).

In our study, the patients who received second-line PTX exhibited a lower transition rate from second- to third-line treatment (27.7%). As regards PS and Alb levels prior to second-line treatment, the general condition of the patients who received second-line PTX was poor prior to second-line chemotherapy. PTX is often selected for patients with peritoneal dissemination, which was frequently the case in the present study. Therefore, we hypothesized that the transition from second- to third-line treatment may be difficult

for patients who receive second-line PTX. However, in the WJOG4007 trials, patients with extensive peritoneal dissemination were excluded (25). Accordingly, the difference in the rate of transition to third-line treatment between the present study and the WJOG4007 trials is likely to be due to differences between the clinical trial setting and the actual clinical setting.

The discontinuation of second- and third-line treatment (Table II) were commonly due to PD and a decrease in the PS, whereas discontinuation due to AEs was observed in only 1 case. Additionally, the majority of treatment doses were 100% in the patients who received second-line PTX or third-line CPT-11 and the general condition of the patients who transitioned to third-line treatment was poor; however, in this study, the incidence of severe AEs was low. Accordingly, we considered second-line PTX and third-line CPT-11 to be tolerable and patients may successfully continue treatment in the actual clinical setting.

As regards AEs following second-line PTX and third-line CPT-11 in patients who received second-line PTX, the frequency of malaise was high (76.9%) with third-line CPT-11. Although malaise is not commonly considered to be a severe AE, it may be perceived as severe if the general condition of the patient is poor. For second-line PTX and third-line CPT-11, the frequency of oligochromemia was high (~77%); however,

Table IV. Reasons for discontinuation with second- and third-line therapy in patients who received second-line CPT-11.

A, Discontinuation following second-line CPT-11				
Variables	Second-line CPT-11 ^a (n=15)		Third-line PTX ^b (n=11)	
Transition rate, % (n/total)	73.3 (11/15)			
Reason for discontinuation				
Adverse events	1		0	
Progressive disease	9		6	
Decrease in PS	4		5	
Others	1		0	
Continuity period, days				
Median (range)	138 (28-566)		110 (17-350)	
Treatment dose, %				
Median (range)	100 (80-100)		100 (100-100)	
B, PS and serum Alb levels				
PS and serum Alb by treatment transition	At the start of second-line CPT-11	At the end of second-line CPT-11	At the end of third-line CPT-11	P-values
PS, value (range)				
Patients who transitioned to third-line treatment	0 (0-1)	0 (0-2)	2 (0-3)	<0.0001
Patients who stopped at second-line treatment	0 (0-2)	3 (1-3)	-	<0.0001
Serum Alb level, g/dl (range)				
Patients who transitioned to third-line treatment	4.2 (3.2-4.9)	4.1 (3.2-4.8)	3.1 (2.1-4.5)	0.0014
Patients who stopped at second-line treatment	3.4 (2.4-4.2)	2.9 (2.6-3.4)	-	0.2217
^a Patients who received irinotecan as second-line treatment; ^b Patients who received paclitaxel as third-line treatment; PTX, paclitaxel; CPT-11 irinotecan; PS, performance status; Alb, albumin.				

this may be attributed to the waning nutritional status of pretreated patients.

In the patients who received second-line CPT-11, the rate of transition from second- to third-line treatment (73.3%) was comparable to that reported in the WJOG4007 study (Table IV). Furthermore, in a previous study conducted by Kawamura *et al* (11), it was reported that if the AEs are mild and the PS is good, third-line treatment is appropriate. In the present study, based on the Alb levels and the PS, the general condition of the patients who were unable to transition to third-line treatment was considered to be poor prior to second-line chemotherapy. In addition, during third-line CPT-11, the general condition of the patients was considered to have further deteriorated.

The majority of the treatment doses were 100% in the patients who received second-line CPT-11 or third-line PTX and severe AEs were infrequent with second-line CPT-11 and third-line PTX, whereas discontinuation due to AEs was reported in only 1 case. A previous study by Farhat (15) reported

that hematological and digestive toxicities were tolerable and mild with irinotecan-based chemotherapy, particularly with a weekly regimen. Therefore, CPT-11 as second-line and PTX as third-line treatment are considered to be tolerable and patients may successfully continue treatment in the clinical setting.

As regards AEs following second-line CPT-11 and third-line PTX in patients who received second-line CPT-11, the frequency of malaise was found to be high (73.3%) with second-line CPT-11, similar to that for third-line CPT-11 in patients who received second-line PTX. The frequency of diarrhea with PTX was higher in the third-line (63.6%) compared to that in the second-line setting (8.5%), possibly due to disease progression.

In the patients who received PTX or CPT-11 as second-line treatment and transitioned to third-line treatment, neutropenia was more frequently observed during second-line compared to that during third-line treatment; these patients were not administered a reduced dose during third-line treatment. A previous study by Shitara *et al* (26) reported a correlation

Table V. Adverse events with second- and third-line therapy in patients who received second-line CPT-11.

Adverse events	Second-line CPT-11 ^a (n=15)		Third-line PTX ^b (n=11)	
	All grades (%)	Grade ≥ 3 (%)	All grades (%)	Grade ≥ 3 (%)
Leucopenia	8 (53.3)	1 (6.7)	3 (27.3)	0 (0.0)
Neutropenia	8 (53.3)	0 (0.0)	3 (27.3)	0 (0.0)
Oligochromemia	8 (53.3)	0 (0.0)	6 (54.5)	1 (9.1)
Thrombocytopenia	1 (6.7)	0 (0.0)	1 (9.1)	0 (0.0)
AST/ALT increase	1 (6.7)	1 (6.7)	0 (0.0)	0 (0.0)
Febrile neutropenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	9 (60.0)	0 (0.0)	5 (45.5)	0 (0.0)
Vomiting	2 (13.3)	0 (0.0)	4 (36.4)	0 (0.0)
Malaise	11 (73.3)	0 (0.0)	5 (45.5)	1 (9.1)
Diarrhea	5 (33.3)	0 (0.0)	7 (63.6)	0 (0.0)
Anorexia	6 (40.0)	0 (0.0)	3 (27.3)	1 (9.1)
Stomatitis	3 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sensory neuropathy	4 (26.7)	0 (0.0)	7 (63.6)	0 (0.0)
Constipation	6 (40.0)	0 (0.0)	5 (45.5)	0 (0.0)
Taste alteration	1 (6.7)	0 (0.0)	1 (9.1)	0 (0.0)
Infusion site extravasation	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	1 (9.1)	0 (0.0)
Hot flushes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Edema	1 (6.7)	0 (0.0)	1 (9.1)	0 (0.0)
Nail discoloration	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	2 (18.2)	0 (0.0)

^aPatients who received irinotecan as second-line treatment; ^bPatients who received paclitaxel as third-line treatment; PTX, paclitaxel; CPT-11, irinotecan; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table VI. Incidence of neutropenia with second- and third-line treatment in patients who transitioned to third-line treatment.

Neutropenia	Second-line PTX ^a		Second-line CPT-11 ^b		Total	
	Second-line PTX	Third-line CPT-11	Second-line CPT-11	Third-line PTX	Second-line treatment	Third-line treatment
Presence	10	2	5	3	15	5
Absence	3	11	7	9	10	20
P-values	0.0016		0.3864		P=0.0039	

^aPatients who received paclitaxel as second-line treatment; ^bPatients who received irinotecan as second-line treatment. PTX, paclitaxel; CPT-11, irinotecan.

between prognosis and the occurrence of neutropenia in patients receiving PTX as second-line treatment. Similarly, there may exist a correlation between prognosis and neutropenia for third-line treatment; therefore, we consider this to be an important focus of future investigations.

In conclusion, second- or third-line treatment with PTX or CPT-11 for patients with advanced or recurrent gastric cancer

has been associated with a low incidence of severe AEs and the patients were able to successfully continue treatment. However, the incidence of diarrhea during treatment with PTX in the third-line setting and that of malaise during treatment with CPT-11 in the second- and third-line setting must be carefully considered when planning chemotherapy for such patients.

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