Non-randomized Comparison Between Irinotecan plus Mitomycin C and Irinotecan Alone in Patients with Advanced Gastric Cancer Refractory to Fluoropyrimidine and Platinum

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Abstract. *Background: Irinotecan alone and plus mitomycin C have been proven to be effective as second-line chemotherapy for advanced gastric cancer. The objective of the present study was to compare the efficacy and safety of irinotecan alone (CA) and with mitomycin C (CM) in clinical practice. Patients and Methods: Between November 2006 and December 2011, 46 patients with advanced gastric cancer refractory to fluoropyrimidine and platinum were treated with CM (n=22) or CA (n=24). Results: Baseline characteristics of the patients were similar in the two treatment groups, with the exception of the sex ratio. The median progression-free survival was 3.9 months in the CM arm and 3.7 months in the CA arm (p=0.25), and the median overall survival was 9.6 and 8.7 months (p=0.36), respectively. The overall response rate was 18% in the CA arm and 9% in the CM arm (p=0.38). Grade 3/4 neutropenia (45% vs. 25%), anemia (36% vs. 4%), febrile neutropenia (14% vs. 8%), anorexia (14% vs. 8%) tended to be higher in the CM arm than in the CA arm. Conclusion: Although the efficacy of CM and CA for advanced gastric cancer refractory to fluoropyrimidine and platinum was not significantly different, CM tended to lead to greater incidence of adverse events in clinical practice.*

Gastric cancer remains one of the most important malignancies worldwide, while being the second leading cause of cancer death (1). In Japan, gastric cancer is the second most common cause of cancer death, with approximately 50,000 deaths annually (2). Surgical resection is curative; however, patients with gastric cancer commonly present with unresectable disease (3). Even after curative surgical resection, 60% of patients eventually experience relapse (4). Outcomes remain very poor for patients with unresectable or recurrent gastric cancer, although survival has been improved by systemic chemotherapy compared to best supportive care alone (5-7).

There is no globally-accepted standard first-line chemotherapy for advanced gastric cancer, but fluoropyrimidine-based and platinum-based combinations with or without a third drug (usually docetaxel or epirubicin) are the most widely used combinations. In Japan, S-1 (tegafur gimeracil oteracil potassium) is an established first-line agent for advanced gastric cancer (8). Recently, an important phase III study of first-line chemotherapy for advanced gastric cancer was reported. The SPIRITS study (S-1 *versus* S-1 plus cisplatin) demonstrated that overall survival (OS) with S-1 plus cisplatin was superior to that with S-1 monotherapy (13.0 *vs*. 11.0 months; p=0.04) (9). On the basis of these results, the combination chemotherapy of S-1 plus cisplatin was regarded as the standard first-line treatment for advanced gastric cancer in Japan.

Irinotecan is a derivative of camptothecin that exerts antitumor activity by inhibiting DNA topoisomerase-1. In a phase II trial, the response rate (RR) to irinotecan alone (CA) was 16% in patients with previously-treated advanced gastric cancer, and the result supports the finding that irinotecan is active against advanced gastric cancer (10). Mitomycin C (MMC) is also effective against advanced gastric cancer. Pre-clinical studies have shown that a combination MMC and irinotecan synergistically inhibits tumor growth *in vitro* (11).

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This is possibly due to the induction of topoisomerase I gene expression by MMC, thereby increasing tumor cell sensitivity to irinotecan. A phase II study of a combination of irinotecan and MMC therapy (CM) led to an overall response rate of 24% and a favorable survival time of 10 months in patients with advanced gastric cancer refractory to fluoropyrimidine, with acceptable tolerability (12). From this finding, CM as second-line chemotherapy for advanced gastric cancer might present a potential treatment option. However, to our knowledge there has been no study directly comparing CM with CA for gastric cancer as second-line treatment. The objective of the present study was therefore to investigate the efficacy and safety of CM and CA in patients with advanced gastric cancer refractory to fluoropyrimidine and platinum.

Patients and Methods

Patients. The source of the data for this study was the database of patients treated in our institutions, which include the Toyama University Hospital, Takaoka City Hospital, and the Kouseiren Takaoka Hospital. We analyzed patients with advanced gastric cancer who received CM or CA as second-line treatment. Eligible patients were those with histologically-confirmed adenocarcinoma of the stomach and those who had disease progression following fluoropyrimidine plus cisplatin therapy. Patients were required to have locally-unresectable disease or metastatic lesions at the time of diagnosis or after curative resection. Patients were also required to have an Eastern Cooperative Oncology Group performance status of 0-2 and adequate bone marrow (leukocyte count, >3500 per mm^3; platelet count, >100,000 per mm^3), liver function [bilirubin <2.0 mg/dl; aspartate aminotransferase/alanine aminotransferase (AST/ALT) <150 U/l], and renal function [creatinine clearance (CCr) >50 ml/min]. Patients with serious complications, clinically significant cardiovascular disease, evidence of central nervous system metastases, massive ascites, or a history of another major type of cancer were also excluded from this study.

Treatment. Patients were treated with CM or CA. The treatment schedule of each therapy was as follows: CM: Irinotecan, at a dose of 150 mg/m^2, given as a 90-min intravenous infusion, and MMC, at a dose of 5 mg/m^2, given as an intravenous bolus on day 1 of a 14-day cycle. CA: Irinotecan, at a dose of 150 mg/m^2, delivered by 90-min intravenous infusion bi-weekly. The total administered dose of MMC had to be less than 50 mg/m^2 to prevent delayed cumulative toxicity, such as hemolytic uremic syndrome and pulmonary fibrosis. When patients were elderly, and had poor performance status, or for other reasons, the dosage of drugs was appropriately reduced according to the judgment of the attending physician. All patients received premedication with serotonin (5-hydroxytryptamine 3) antagonists and dexamethasone. Treatment was repeated until disease progression, the occurrence of unacceptable toxicity, or the patient's refusal to continue therapy.

Statistical analysis. The RR was evaluated in patients who had measurable lesions using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 (13). Adverse events were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (14). The survival time was calculated from the date of treatment initiation to the day on which events were confirmed, or to the last date of confirmation of survival. We estimated survival curves using the Kaplan–Meier method and compared them with the log-rank test. The unpaired chi-square test or Student's *t*-test was used for the comparison between groups. All statistical analyses were performed by using JMP version 10 (SAS Institute, Cary, NC, USA), and *p*-values of <0.05 (two-sided) were considered to indicate statistical significance.

Results

Patients' characteristics. Between November 2006 and December 2011, 46 patients with gastric cancer met the criteria and were included in the analysis. Among them, 22 patients (49%) received CM and 24 patients (51%) received CA. Table I shows patients' characteristics and treatment exposure. Demographic and baseline disease characteristics of the patients were similar in the two treatment groups except for sex ratio. Regarding prior treatment, 15 (68%) patients in the CM arm and 10 (42%) in the CA arm had undergone S-1 plus cisplatin therapy, six (27%) patients in the CM arm and 11 (46%) in the CA arm had undergone S-1 plus ciaplatin and docetaxel therapy, and two (8%) patients in the CA arm had undergone capecitabin plus cisplatin and trastuzumab therapy. The remaining patients, whose primary tumor was located at the esophagogastric junction, received 5-FU plus cisplatin therapy. The median number of treatment cycles was six in the CM arm (range=2-10) and seven in the CA arm (range=1-76). The number of treatment discontinuations was 22 (100%) in the CM arm and 23 (96%) in the CA arm for the following reasons: disease progression in 19 (86%) in the CM arm and 20 (87%) in the CA arm; adverse events in three (14%) in the CM arm and 2 (9%) in the CA arm; and change of hospital in one (4%) in the CA arm. After the end of the second-line treatment, third-line treatments were given to 19 out of 22 (86%) of those of the CM arm and 18 out of 23 (78%) patients in the CA arm.

Response and survival. The median progression-free survival (PFS) was 3.9 months in the CM arm and 3.7 months in the CA arm (p=0.25) (Figure 1A). The median OS for the CM arm and CA arm was 9.6 months and 8.7 months (p=0.36), respectively (Figure 1B). The objective RRs among patients with measurable disease are shown in Table II. No patients had a complete response. The overall RR was 19% in the CM arm and 10% in the CA arm (p=0.38), and the disease control rate was 86% in the CM arm and 62% in the CA arm (p=0.08).

Adverse events. Adverse events are summarized in Table III. Treatment was generally well-tolerated in each group. Patients receiving CM experienced higher frequencies of febrile neutropenia, neutropenia, anemia, and thrombocytopenia than those receiving CA. In the CM arm, acute interstitial pneumonia occurred in one patient who was responsive to steroid treatment. There were no treatment-related deaths.

Table I. *Patients' characteristics and treatment.*

	CM arm (n=22)	CA arm (n=24)	*p*-Value
Age, years			
Median	62	65	0.19
Range	49-73	47-80	
Gender, no. (%)			
Male	20 (91)	15 (63)	0.024
Female	2 (9)	9 (37)	
ECOG performance status score, no. (%)			
0	9 (41)	8 (33)	0.70
1	11 (50)	16 (67)	
2	2 (9)	0 (0)	
Histology, no. (%)			
Intestinal	14 (64)	11 (46)	0.22
Diffuse	8 (36)	13 (54)	
No. of metastatic sites involved, no. (%)			
1	2 (9)	5 (21)	0.27
≥2	20 (91)	19 (79)	
Prior chemotherapy, no. (%)			
SP	15 (68)	10 (42)	0.22
DCS	6 (27)	11 (46)	
FP	1 (5)	1 (4)	
XP plus Tmab	0 (0)	2 (8)	
Third-line chemotherapy, no. (%)			
Received	19 (86)	18 (78)	0.48
Treatment cycles			
Median	6	7	0.30
Range	2-10	1-76	
Treatment discontinuation, no. (%)			
Total	22 (100)	23 (96)	
Disease progression	19 (86)	20 (87)	0.83
Adverse events	3 (14)	2 (9)	
Change of hospital	0 (0)	1 (4)	

ECOG, Eastern Cooperative Oncology Group; SP, S-1 (tegafur/gimeracil/oteracil potassium) +cisplatin; DCS, docetaxel+cisplatin+S-1; FP, 5-Fluorouracil+cisplatin; XP+Tmab, capecitabine+cisplatin+trasutuzumab.

Table II. *Objective responses.*

	CM arm (n=21)	CA arm (n=21)
Could not be evaluated	1	3
Response, no. (%)		
Complete	0 (0)	0 (0)
Partial	4 (19)	2 (10)
Stable disease	14 (67)	11 (52)
Progressive disease	3 (14)	8 (38)
Rate of objective response*		
No. (%)	4 (19)	2 (9)
95% CI	2.2-35.8	0-21.2
	p=0.38	
Disease control rate**		
No. (%)	18 (86)	13 (62)
95% CI	71.1-100	41.2-82.8
	p=0.08	

CI, Confidence interval. *The rate of objective response was defined as the total percentage of patients who had a complete or partial response. **The disease control rate was defined as the total percentage of patients who had a complete or partial response or stable disease.

Table III. *Toxicity due to therapy [no. (%)].*

	CM arm (n=22)		CA arm (n=24)	
	All	Grade 3/4	All	Grade 3/4
Hematological				
Leukopenia	21 (95)	6 (27)	18 (75)	6 (25)
Neutropenia	21 (95)	10 (45)	19 (79)	6 (25)
Anemia	22 (100)	8 (36)	21 (88)	1 (4)
Thorombocytopenia	13 (59)	2 (9)	7 (30)	2 (8)
Non-hematological				
Anorexia	18 (82)	3 (14)	16 (67)	2 (8)
Vomiting	6 (27)	0 (0)	3 (13)	0 (0)
Diarrhea	14 (64)	1 (4.5)	10 (47)	1 (4)
Fatigue	20 (91)	0 (0)	16 (67)	1 (4)
Pneumonitis	1 (5)	0 (0)	0 (0)	0 (0)
Febrile neutropenia	3 (14)	3 (14)	2 (8)	2 (8)

According to the Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 (14).

Discussion

Two randomized phase III trials compared second-line chemotherapy with best supportive care alone in patients with advanced gastric cancer. Irinotecan monotherapy and docetaxel monotherapy were demonstrated to be superior to best supportive care in terms of OS, indicating that second-line chemotherapy is beneficial for this indication (15, 16). In Japan, the WJOG4007 trial (irinotecan *vs* paclitaxel) did not demonstrate irinotecan superiority compared to paclitaxel in OS for patients with advanced gastric cancer refractory to fluoropyrimidine and platinum (17). However, irinotecan was considered a potential treatment option together with paclitaxel.

The current retrospective study evaluated the efficacy and safety of chemotherapy with CM and CA in patients with advanced gastric cancer refractory to fluoropyrimidine and platinum in clinical practice. The survival outcome was at the same level as previous reports and the survival effect of the two treatments was equivalent: the median PFS and median OS were 3.9 months and 9.6 months in the CM arm and 3.7 months and 8.7 months in the CA arm, respectively. Comparing the two groups, CM was superior in the disease control rate. However, this was not statistically significant.

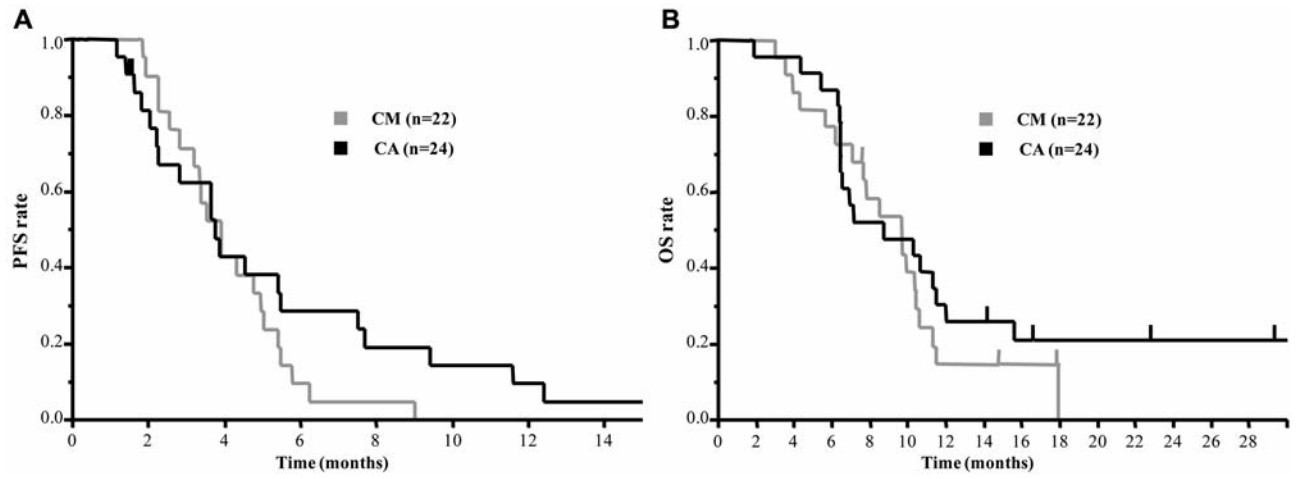

Figure 1. *Kaplan–Meier estimates of progression-free survival (PFS) (A) and overall survival (OS) (B) according to treatment group. The median PFS was 3.7 months in the CA arm and 6.7 months in the CM arm. There were no statistical differences between the two arms (p=0.25). The median OS was 8.7 months in the CA arm and 9.6 months in the CM arm. There were no statistical differences between the two arms (p=0.36).*

The response rate in this study was less impressive compared with the previous phase II or phase III study in Japan (12, 17). There are several reasons which may account for this, the first being the differences in first-line chemotherapy. In the phase II study of CM, most patients were given 5-FU-based monotherapy (*i.e.* 5-FU monotherapy, 40%; S-1 monotherapy, 33%; S-1 plus cisplatin, 13%; and methotrexate plus 5-FU, 4%) (12). In our study, all patients had previously received fluoropyrimidine plus cisplatin. Secondly, the differences in the background characteristics of the patients at the initiation of second-line chemotherapy might have reduced the RR in our study: the performance status of our patients was poorer than that of patients in previous studies.

The incidences of grade 3 or higher toxic effects were as follows: leucopenia, 27% and 25%; neutropenia, 45% and 25%; anemia 36% and 4%; anorexia, 14% and 8%; febrile neutropenia, 14% and 8%, in the CM and CA arms, respectively. The incidence rate in this clinical practice was consistent with those in previous clinical trials (12, 17). Although the CM arm tended to have greater incidence of adverse events than the CA arm, treatment was generally well-tolerated and adverse events were manageable in both groups.

Third-line chemotherapy was given to 19 patients in the CM arm and 18 patients in the CA arm, while three patients and five patients respectively, received best supportive care. Taxane-based chemotherapy was performed for 16 patients in the CM arm and 18 patients in the CA arm. The frequency of the patients who received third-line chemotherapy was at the same level as previous trials (17). This suggests that taxane-based chemotherapy can be an option even if the irinotecan based chemotherapy was previously performed in clinical practice.

This study had limitations because it was retrospective and a selection bias may exist due to the small number of patients, not randomized to treatment arms. Although there were no statistical differences between the two arms in baseline characteristics, the patients who had better general status could have been administered CM because a greater incidence of adverse events had been anticipated in this treatment group. This bias may operate in favor of CM.

In conclusion, our study showed that CM and CA were modestly active and safe in patients with advanced gastric cancer refractory to fluoropyrimidine and platinum in clinical practice. The efficacy of CM and CA was not significantly different in terms of survival rates, moreover CM tended to give greater incidence of adverse events. Although this study had limitations, the addition of MMC to irinotecan did not seem to be beneficial for the specific patient population.

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