Gastric Cancer (2011) 14:226–233
DOI 10.1007/s10120-011-0030-8

ORIGINAL ARTICLE

A phase II study of biweekly mitomycin C and irinotecan combination therapy in patients with fluoropyrimidine-resistant advanced gastric cancer: a report from the Gastrointestinal Oncology Group of the Japan Clinical Oncology Group (JCOG0109-DI Trial)

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Received: 26 October 2010 / Accepted: 24 January 2011 / Published online: 19 April 2011

Abstract
Background Preclinical studies have shown that mitomycin C (MMC) acts synergistically with irinotecan (CPT-11). In this phase II study, we evaluated the efficacy and toxicity of MMC/CPT-11 therapy as second-line chemotherapy for patients with fluoropyrimidine-resistant advanced gastric cancer.
Methods Eligible patients had evidence of tumor progression despite prior treatment with fluoropyrimidine-based regimens or had relapsed within 6 months after completion of therapy with adjuvant fluoropyrimidines. Treatment consisted of MMC (5 mg/m^2) and CPT-11 (150 mg/m^2) administered i.v. every 2 weeks. The primary endpoint was the response rate (RR). Our hypothesis was that this combination therapy was efficacious when the lower boundary of the 95% confidence interval (CI) of the RR exceeded 20% of the threshold RR.

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Results Between April 2002 and July 2003, 45 eligible patients were registered and analyzed. Among the 45 patients, 40 (89%) had previously received chemotherapy for metastasis and 24 (53%) had a performance status (PS) of 0. Thirteen partial responses were obtained among the 45 patients, resulting in an overall RR of 29% (95% CI, 16–42%). The median time to progression was 4.1 months, and the median survival time was 10 months, with a 1-year survival rate of 36%. Grade 4 neutropenia was observed in 29% of the patients, whereas febrile neutropenia occurred in 9%. The incidence rates of grade 3 nausea and diarrhea were 13 and 2%, respectively.

Conclusions Although this study did not achieve the per-protocol definition of activity, the progression-free survival and overall survival appeared to be promising, with acceptable tolerability. Thus, MMC/CPT-11 therapy as second-line chemotherapy for fluoropyrimidine-resistant advanced gastric cancer presents a potential treatment option in patients with a good PS.

Keywords Gastric cancer · Mitomycin-C · Irinotecan · Fluoropyrimidine-resistant · Second-line chemotherapy

Introduction

Gastric cancer is the most common malignancy in Asian countries, with approximately 50,000 deaths in Japan annually [1]. The treatment of choice for this malignancy is primary tumor resection. In patients with curatively resected stage I–III gastric cancer, the 5-year survival proportion is >50%; however, this proportion remains at <10% in stage IV or recurrent disease. Randomized trials have demonstrated that fluorouracil-based regimens improve survival proportions in patients with advanced gastric cancer (AGC) compared with best supportive care (BSC) alone as first-line chemotherapy [2–4]. Moreover, combination chemotherapy results in superior outcomes compared with monotherapy. In Japan, the efficacy and toxicity of the combination of an oral fluoropyrimidine (S-1) and platinum was previously evaluated in the phase III SPIRITS (S-1 plus cisplatin vs. S-1 alone for first-line treatment of AGC) trial. S-1 plus cisplatin resulted in superior overall survival (OS) compared with S-1 alone [hazard ratio (HR), 0.77; 95% confidence interval (CI), 0.61–0.98%; $P = 0.04$], with an impressive median OS of 13.0 months [5]. The Japan Clinical Oncology Group (JCOG) 9912 trial (5-fluorouracil [FU] alone vs. S-1 alone vs. irinotecan [CPT-11] plus cisplatin [CDDP] combination for the first-line treatment of AGC) was also conducted in Japan. S-1 showed significant noninferiority for progression-free survival (PFS) and OS compared with 5-FU alone; however, CPT-11 plus CDDP showed no significant superior effects on PFS and OS compared with 5-FU alone [6]. In Japan, S-1 plus CDDP combination therapy is considered the standard first-line treatment for AGC.

Thuss-Patience et al. [7] reported at the 2009 Annual Meeting of the American Society of Clinical Oncology (ASCO) that CPT-11 monotherapy significantly prolonged OS compared with BSC as second-line chemotherapy. Although that report was the first randomized phase III study investigating second-line chemotherapy for AGC, no objective responses were observed. Thus, a consensus regarding the standard regimen for second-line chemotherapy has not yet been obtained.

Many AGC patients who failed to respond to first-line chemotherapy showed symptoms of pain, weight loss, or nausea due to their progressive disease. Thus, the induction of a tumor response is as important as delaying tumor progression for as long as possible. Patients who received combination chemotherapy showed higher response rates than those who received single-agent chemotherapy alone. Therefore, combination chemotherapy is preferable to single-agent chemotherapy for palliation. Moreover, combination chemotherapy may prolong OS compared with single-agent chemotherapy alone.

CPT-11 is a potent topoisomerase I inhibitor and is effective against AGC. In a phase II trial, the response rate (RR) to CPT-11 alone was 16% in previously treated AGC patients [8]. The administration of a CDDP and CPT-11 combination in AGC patients resulted in a higher RR and longer time to progression (TTP) [9–11]. As mentioned above, CDDP/CPT-11 did not significantly prolong OS over 5-FU, but induced a significantly higher RR than 5-FU in the JCOG9912 trial [6]. A 5-FU, leucovorin (LV), and CPT-11 combination produced a higher RR and longer TTP than CDDP/CPT-11 in AGC patients [12]. In another randomized phase III trial, 5-FU/LV/CPT-11 showed a trend to have superiority in TTP over CDDP/5-FU (5.0 vs. 4.2 months, respectively; HR, 1.23; 95% CI, 0.97–1.57%; $P = 0.088$), and a better safety profile [13]. These results support the finding that CPT-11 is active against AGC.

Mitomycin C (MMC) is also effective against AGC. Preclinical studies have shown that a MMC and CPT-11 combination synergistically inhibits tumor growth in vitro [14]. This is due to the possible induction of topoisomerase I gene expression by MMC, thereby increasing tumor cell sensitivity to CPT-11. A phase I/II study of this combination recommended an MMC dose of 5 mg/m^2 and a CPT-11 dose of 150 mg/m^2 administered biweekly [15]. The dose-limiting toxicities of this combination regimen when administered at 10 mg/m^2 for MMC and 150 mg/m^2 for CPT-11 were grade 4 neutropenia with or without febrile neutropenia and grade 3 diarrhea. The overall RR was 50% (15/30 patients), and 5 of 14 patients (36%) with prior chemotherapy showed a partial response (PR). We

previously showed that MMC and CPT-11 combination chemotherapy was effective and well tolerated in patients with fluoropyrimidine-resistant metastatic colorectal cancer; the RR, median TTP, and median survival time (MST) were 34% (95% CI, 20–49%), 4.2 months, and 11.9 months [16], respectively.

These results led us to conduct the present phase II clinical trial to investigate the efficacy and toxicity of MMC/CPT-11 therapy in patients with AGC resistant to a fluoropyrimidine-containing regimen in the JCOG0109-DI study.

Patients and methods

Eligibility

A patient was considered eligible if there was evidence of a refractory response to one prior chemotherapy containing fluoropyrimidine, which was any of the following types of history of chemotherapy:

1. In the case of unresectable gastric cancer, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine, or confirmed immediately after the discontinuation for any reason other than disease progression.
2. In the case of recurrent gastric cancer, recurrence detected within 24 weeks from the last dose of postoperative adjuvant chemotherapy containing fluoropyrimidine, and further chemotherapy was not administered after recurrence.
3. In the case of recurrent gastric cancer detected 25 weeks after the last dose of postoperative adjuvant chemotherapy, disease progression detected while receiving front-line chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after the discontinuation for any reason other than progression.
4. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the effect of neoadjuvant chemotherapy containing fluoropyrimidine was stable disease, progressive disease, or not evaluated, and recurrence was identified after curative resection. Chemotherapy was not performed following recurrence.
5. In the case of recurrent gastric cancer treated with neoadjuvant chemotherapy, the chemotherapy effect was a complete response or PR, and progression was detected during one chemotherapy containing fluoropyrimidine after recurrence, or confirmed immediately after discontinuation for any reason other than progression.

Disease progression and the nonefficacy of neoadjuvant chemotherapy were believed to represent clinical failure by treating physicians. Elevation of the level of a tumor marker, such as carcinoembryonic antigen (CEA), was not accepted as adequate evidence for treatment failure. Documentation of evidence of a refractory response by computed tomography (CT) and magnetic resonance imaging was required.

For the other eligibility criteria, patients must be between 20 and 75 years of age, and have an Eastern Cooperative Oncology Group performance status (PS) of 0 to 2, adequate baseline bone marrow function [white blood cell (WBC) and platelet counts $\geq$4,000 and 100,000/mm^3, respectively], adequate hepatic function (serum bilirubin level $\leq$1.5 mg/dl and both serum aspartate aminotransferase and alanine aminotransferase levels $\leq$100 U/l), adequate renal function (serum creatinine level $\leq$1.5 mg/dl), adequate respiratory function (arterial partial pressure of oxygen $\geq$70 mmHg), and have received no blood transfusion within 14 days before enrollment. All patients were required to have $\geq$1 measurable lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST).

Patients were excluded if they had symptomatic brain metastasis, symptomatic ascites and/or pleural effusion, previous history of MMC or CPT-11 chemotherapy, pre-existing diarrhea of >4 times/day, suspicion of existing active bleeding which needed blood transfusion at 14 days prior to registration in this study, or a high risk of a poor outcome due to concomitant nonmalignant disease (i.e., cardiac, pulmonary, renal, or hepatic disease; poorly controlled diabetes; or uncontrolled infection), or severe psychiatric disease. Pregnant or lactating women were excluded.

The study protocol was approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating hospital. All patients gave their written informed consent.

Treatment plan

The treatment schedule consisted of one MMC dose (5 mg/m^2, bolus injection), then CPT-11 (150 mg/m^2, 90-min i.v. infusion) repeated every 2 weeks, as described previously [16]. All patients were treated on an outpatient basis and were recommended to receive both a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone to prevent emesis. Subsequent treatment cycles were withheld until the WBC and platelet counts were $\geq$3,000 and 100,000/mm^3, respectively; diarrhea was $\leq$grade 1; and there were no infection symptoms such as pyrexia ($\geq$38°C). When the treatment course was delayed within 8 days from the planned schedule, the same dosage levels as those used previously were administered. When the treatment course was delayed beyond 8 days and within 21 days from the planned schedule, one lower dose level (CPT-11 level -1,

125 mg/m^2; level -2, 100 mg/m^2) than the previous level was administered, while the MMC dose was maintained at 5 mg/m^2. The treatment course was discontinued if it could not be started within 21 days from the planned schedule. When grade 4 leukopenia or thrombocytopenia occurred in a previous treatment course causing a delay within 8 days, the same dosage levels as those used previously were administered. When grade 2 diarrhea or higher was observed in a preceding course, dosages 1 level lower than the previous dosages were administered.

Treatment was repeated until disease progression or when severe toxicity was observed. The total MMC dose was limited to 50 mg/m^2, to prevent cumulative toxicity (e.g., interstitial pneumonia and hemolytic uremic syndrome), and thereafter CPT-11 alone was administered. This indicates that the maximum number of total treatment cycles of MMC/CPT-11 therapy is 10 cycles.

Evaluation of response and toxicity

During protocol treatment, the patient's signs and symptoms, as well as laboratory data (i.e., WBC with differential counts, liver function tests, urea nitrogen, creatinine, electrolytes, and urinalysis) were examined biweekly. Adverse events were evaluated using the National Cancer Institute-Common Toxicity Criteria version 2.0. Tumor response was assessed by CT every 4 weeks. The response of measurable and evaluable disease sites was assessed by each investigator in accordance with RECIST, and then reviewed by central review at the group meeting.

Statistical analysis

For this study, the primary endpoint was the RR and the secondary endpoints were OS and toxicity. Here, we used the standard design (attained design) of the Southwest Oncology Group [17]. Based on reports of RRs of 22% with paclitaxel alone [18] and 16% with CPT-11 alone [8] in the second-line setting and an RR of 36% in phase I/II studies of MMC/CPT-11 therapy [15], the RR in this study was expected to be within 30–40% for a future phase III trial. Here, the required sample size was calculated to be 45 patients, with the following parameters: $\alpha = 0.05$, $\beta = 0.10$, threshold response rate $(p_0) = 20\%$, and expected response rate $(p_a) = 40\%$. Interim analysis was performed when the number of enrolled subjects reached 25. The significance level for the interim analysis was set as $P < 0.02$. Furthermore, when the number of patients who reached RR was <5 at the interim analysis, the study was prematurely discontinued because it would have been difficult to exceed the expected RR despite further patient accumulation, or because it would not be worth advancing this regimen to an ensuing clinical study. When the study was not completed after the interim analysis, the number of patients was increased to 45 in order to allow the null hypothesis (threshold RR) to be tested. When α was <0.05, or when the lower boundary of the 95% CI of the RR exceeded 20% of the threshold RR, this therapy was considered to be efficacious as chemotherapy for gastric cancer patients who had received pretreatment. That is, when ≥16 of 45 patients had a PR, this study was judged to be positive. Here, patient enrollment was not temporarily discontinued.

OS was defined as the time from the registration date to death as a result of any cause. PFS was defined as the time from the registration date to the first documentation of objective tumor progression. Time-to-event and OS data were summarized using the Kaplan–Meier method.

Results

Patient population and study treatment

Between April 2002 and July 2003, 45 patients (33 men, 12 women) from 12 hospitals were enrolled and analyzed. Table 1 shows the demographic data, baseline disease, and regimens of prior chemotherapy. The median age was 64 years (range 36–75), and all patients had a good PS of 0 or 1. Eighteen patients (40%) had diffuse-type gastric cancer. As for prior chemotherapy, 40 (89%) had previously received chemotherapy for metastasis, whereas 5 had received adjuvant chemotherapy. In the first-line chemotherapy, 33 patients (73%) had received 5-FU or S-1 alone.

In all 45 patients, MMC/CPT-11 therapy was administered 281 times, and the median number of doses was 6 (range 1–10). Of the 45 patients, 10 (22%) completed the planned 10 chemotherapy cycles. In the remaining 35 patients, the reasons for treatment discontinuation were disease progression in 25, toxicity in 6, patient's refusal in 3, and death in 1. Regarding CPT-11 administration, 11 patients (24%) required -1 level dose reduction and 8 (18%) required -2 level reduction because of leukopenia and thrombocytopenia.

Efficacy

Of the 45 patients, 13 showed a PR (RR: 28.9%; 95% CI, 15.6–42.1%) (Table 2). The median PFS was 4.1 months (Fig. 1). The median OS time was 10.1 months (95% CI, 7.3–12.6 months), and the 1-year survival rate was 38% (Fig. 2).

Because the lower boundary of the 95% CI of the RR (15.6%) did not exceed the threshold RR (20%), the

Table 1 Patient characteristics ($n = 45$)

Age (years)	
Median	64
Range	36–75
Gender	
Male	33
Female	12
ECOG performance status	
0	24
1	21
2	0
Borrmann macroscopic type of primary cancer	
0	1
1	1
2	17
3	18
4	5
Unknown	3
Histological type	
Intestinal	25
Diffuse	18
Unclassified	2
Prior chemotherapy	
5-FU alone	18
S-1 alone	15
S-1 + CDDP	6
MTX + 5-FU	2
Others	4

ECOG Eastern Cooperative Oncology Group, *5-FU* 5-fluorouracil, *CDDP* cisplatin, *MTX* methotrexate

Table 2 Evaluation of response ($n = 45$)

Tumor response	Patients	
	n	% (95% CI)
Complete response	0	0
Partial response	13	28.9 (15.6–42.1)
Stable disease	17	37.7 (23.6–51.9)
Progressive disease	14	31.1 (17.6–44.6)
Not evaluated	1	4.4 (0–6.5)
Survival	Months (95% CI)	
PFS	4.1 M (2.5–5.7)	
OS	10.1 M (7.3–12.6)	

CI confidence interval, *PFS* progression-free survival, *OS* overall survival

MMC/CPT-11 combination as second-line chemotherapy could not be definitively concluded as efficacious for further investigation.

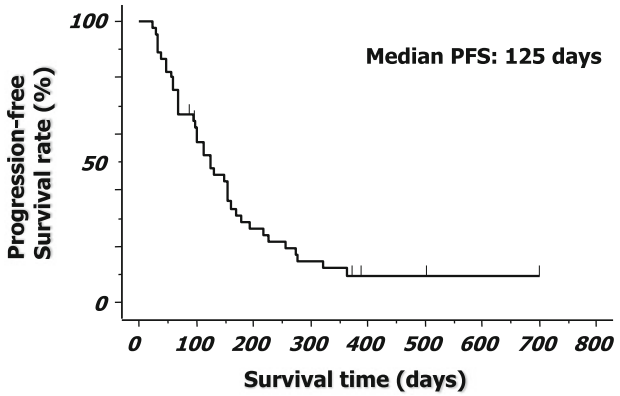

Fig. 1 Kaplan–Meier estimates of progression-free survival (*PFS*) rates

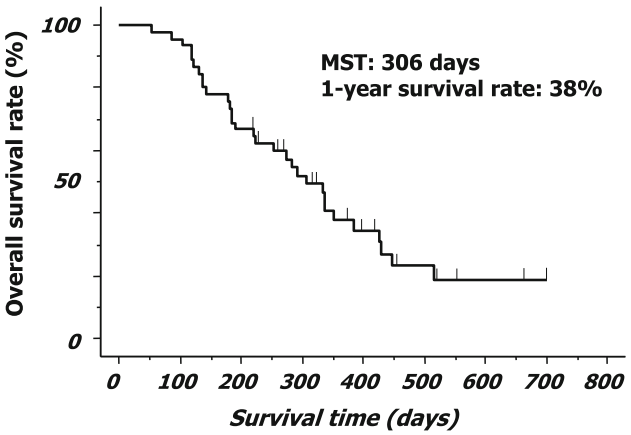

Fig. 2 Kaplan–Meier estimates of overall survival. *MST* Median survival time

Toxicity

The toxicities of the MMC/CPT-11 therapy are summarized in Table 3, with myelosuppression and gastrointestinal toxicity as major toxicities. Grade 3 and 4 neutropenia occurred in 24 and 29% of the patients, respectively, whereas grade 3 and 4 thrombocytopenia developed in only 7%. As for the nonhematological toxicities, the incidence rate of grade 3 diarrhea was 2%, and nausea and vomiting were mild. Early death due to interstitial pneumonitis within 30 days from the last chemotherapy occurred in 1 patient, which was considered by the JCOG Data and Safety Monitoring Committee to have been possibly related to the treatment.

Discussion

In second-line chemotherapy for AGC, the potential benefits remain unclear because of the few prospective studies that have been conducted thus far. These trials demonstrated that

Table 3 Grade 2–4 adverse events according to NCI-CTC ver. 2.0 ($n = 45$)

	Grade 2	Grade 3	Grade 4	Grade 3–4 (%)
Hematological WBC	24	8	5	29
Neutrophils	10	11	13	53
Hb	25	3	3	13
Platelets	1	2	1	7
Febrile neutropenia	0	4	0	9
Non-hematological Anorexia	13	11	0	24
Nausea	11	6	0	13
Diarrhea	4	1	0	2
Infection with grade 3/4 neutropenia	0	2	0	4
Infection without neutropenia	4	2	0	4

NCI-CTC National Cancer Institute-Common Toxicity Criteria, *Hb* hemoglobin

the RRs to second-line chemotherapy in phase II trials for gastric cancer were similar to those observed for other cancers which are more commonly treated after the failure of first-line chemotherapy. Furthermore, 2 Japanese randomized trials (i.e., SPIRITS [5] and JCOG9912 [6]) achieved a median OS of 13.0 months despite the relatively short median PFS of about 4–6 months. Although both JCOG9912 and our previous phase III study (JCOG9205 [19]) utilized 5-FU continuous infusion (c.i.) and 5-FU/CDDP, the obtained median PFS was 2 months and the OS in JCOG9912 was much longer than that in JCOG9205. In the present study, the proportion of patients who received second-line chemotherapy was >70%, which is higher than that obtained in our previous study (53%). The results of previous phase II trials consistently suggest that patients treated with second-line chemotherapy may survive longer than those provided with BSC, although the survival benefit of the second-line chemotherapy has not yet been clarified.

According to the 26 prospective phase II studies reported in the literature, obtained using the search expressions "gastric cancer" and "second-line chemotherapy" in PubMed, the average and median RRs were 18.8 and 20.0% (0–34.6%), respectively [18, 20–44]. Although the present study did not disprove the null hypothesis about RR, it is suggested that MMC/CPT-11 therapy with an RR of 28.9% may possess some antitumor activity as second-line chemotherapy.

As for survival, the present study showed a median survival time of 10.1 months (95% CI, 7.3–12.9 months), and a 1-year survival proportion of 38%. These data are similar to those obtained in the first-line chemotherapy setting and appeared to be better than those obtained using several other regimens, showing a survival period of 3.5–13 months compared with the reported median survival period of 7–10 months in untreated patients. However, it is very difficult to compare phase II studies due to differences in patient background and subsequent therapy. One reason for improved survival may be good clinical selection of a patient. At the baseline evaluation, the median age of the patients in the present study was 64 years (range, 36–75), and all the patients had a good PS of 0 or 1. Another reason for the improved survival was the high proportion of tumor stabilization (66.7%) after the administration of the MMC/CPT-11 regimen. Therefore, it is considered that MMC/CPT-11 therapy may provide some survival benefit.

The toxicity of the MMC/CPT-11 regimen can be considered tolerable and manageable. Hematological toxicity was within the expected range, including grade 4 neutropenia, observed in 13 patients (29%) and grade 3 febrile neutropenia in 4 patients (9%). According to a Japanese prospective pharmacogenomic study of CPT-11, homozygotes and double heterozygotes of *6 and *28 (*6/*6, *28/*28 and *6/*28) were significantly associated with severe neutropenia. The UGT1A1 gene test prior to receiving this regimen may be useful to decide the starting dose of CPT-11 or to decide whether the patient should receive CPT-11 and MMC combination chemotherapy or CPT-11 monotherapy [45]. Although treatment-related death was observed in 1 patient (2%) in the present study, the occurrence of adverse events was similar to that in JCOG9911-DI, a phase II study of the same regimen for colon cancer; thus, MMC/CPT-11 therapy was considered tolerable. In the present study, the proportion of patients with toxicity was similar to that of patients where MMC/CPT-11 therapy was used as second-line treatment against colorectal cancer [16].

From the above results, the present phase II study of MMC/CPT-11 therapy for FU-based chemotherapy-refractory gastric cancer is judged to be negative on the basis of the decision rule defined in the protocol. This may be due to the threshold RR being set very high owing to the lack of data as the basis for setting the threshold level and expected RR, because of the small number of phase II studies of second-line treatment when this protocol was developed. In fact, the RR cannot be considered poor compared with that in phase II studies performed in other treated patients (as shown in Table 2), with a favorable

survival time of 10 months. In conclusion, the MMC/CPT-11 regimen might be one treatment option for pretreated AGC in patients with good PS.

Acknowledgments This study was supported by a Grant-in-Aid for Cancer Research from the Japanese Ministry of Health, Labour and Welfare. We thank Ms. M. Kobayashi and Ms. M. Shinogi for data management and Ms. H. Orita for her secretarial assistance.

Conflict of interest None.

Appendix

Investigators in participating institutions: Yamagata Prefectural Central Hospital, H. Saito; Tochigi Cancer Center, H. Fuji; Saitama Cancer Center, K. Yamaguchi; National Cancer Center Hospital East, T. Doi; Chiba Cancer Center Hospital, T. Denda; National Cancer Center Hospital Tokyo, Y. Shimada; Kitasato University East Hospital, W. Koizumi; Aichi Cancer Center Hospital, Y. Inaba; Nagoya Medical Center, H. Iwase; Osaka Medical College, H. Takiuchi; National Hospital Organization Shikoku Cancer Center, J. Nasu; Kumamoto Regional Medical Center Hospital, M. Yoshida.

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