Mitomycin C plus S-1 as second-line therapy in patients with advanced gastric cancer: a noncomparative phase II study

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S-1 is an oral fluoropyrimidine consisting of the 5-fluorouracil prodrug tegafur combined with two modulating substances, gimeracil and potassium oxonate. On the basis of the potential additive effect between mitomycin C (MMC) and 5-fluorouracil as a continuous infusion, we conducted a phase II study to assess the efficacy and tolerability of the combination of S-1 and MMC as second-line chemotherapy for advanced gastric cancer (AGC). Patients with measurable AGC, progressive after one prior chemotherapy for metastatic disease, received MMC (7 mg/m^2) on day 1 and S-1 (40 mg/m^2) twice daily as an intermittent regimen of 4 weeks of treatment followed by a 2-week rest. Treatment was repeated every 6 weeks. The primary objective was the response rate. For 43 patients registered, 42 patients were treated with MMC plus S-1. A total of 121 chemotherapy cycles were delivered (median: 2; range: 1–6). The patients' median age was 53 years (range: 31–75) and nine (21%) had an Eastern Cooperative Oncology Group performance status of 2. In an intent-to-treat analysis, nine patients (21%) achieved an objective response, which was maintained for 4.1 months. The median progression-free and overall survivals were 3.4 months (95% confidence interval: 2.3–4.5) and 8.0 months (95% confidence interval: 6.1–9.9), respectively. Although fatigue was the most frequently encountered toxicity safety profiles were generally predictable and manageable. One patient developed hemolytic anemia, which was resolved spontaneously. Grade $\geq$ 2 hand–foot syndrome was observed in only three patients. Second-line chemotherapy with MMC and S-1 is an active and tolerable regimen for AGC patients with good performance status. ***Anti-Cancer Drugs*** **19:303–307 © 2008 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Gastric cancer remains the most commonly occurring malignancy in Korea [1]. For patients with unresectable, recurrent, or advanced gastric cancer (AGC), chemotherapy can provide significant palliation of symptoms [2,3]. Over half of patients with AGC who received chemotherapy, however, failed to achieve response, and even in these responders the duration of responses was as short as a few months [4]. Furthermore, the treatment of AGC patients after failure with first-line chemotherapy remains controversial. Patients who fail to respond or have relapse after first-line chemotherapy have a grim prognosis and a standard salvage treatment is not available.

S-1 is a new oral fluoropyrimidine, in which tegafur has been combined with gimeracil and potassium oxonate, and has been reported to have encouraging first-line treatment efficacy with mild toxicity in patients with AGC [5]. The activity observed with S-1 in the phase II studies is at least equivalent, if not better, than continuous infusion and bolus 5-fluorouracil (5-FU) and the other oral fluoropyrimidines. Although S-1 has not been compared with other 5-FU prodrugs to prove similar activity, phase II studies have demonstrated that an objective response could be achieved with second-line treatment with S-1 [6]. The response rate obtained with S-1 monotherapy for patients with prior chemotherapy, however, was as low as 12.5% [7]. An evident need exists to develop new chemotherapeutic regimens that may improve these results.

Similar to 5-FU, to enhance the efficacy of S-1 treatment, various combination regimens have been studied in AGC patients. Mitomycin C (MMC) is traditionally considered an active drug against gastric cancer [8]. In addition, MMC has demonstrated synergistic activity with 5-FU

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and has a mild, predominantly hematologic toxicity [9–11]. It is not associated with stomatitis or diarrhea, and thus is usually combined with 5-FU when used as initial treatment. Until the late 1990s, MMC/5-FU combinations were one of the most important modes of chemotherapy in gastrointestinal cancers [12,13]. In a phase III study [13], there was no significant difference in severe hematologic or nonhematologic toxicities between MMC/5-FU and 5-FU-alone arms. The experience so far concludes that its role as salvage treatment, particularly in combination with oral fluoropyrimidines such as S-1, requires further investigation [14]. Accordingly, this phase II study was conducted to evaluate the efficacy and safety of MMC plus S-1 combination in patients with AGC who failed after first-line chemotherapy.

Patients and methods

Eligibility criteria included measurable AGC, progressive after one prior chemotherapy for metastatic disease, age ≤ 75 years, Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, adequate bone marrow, hepatic and renal functions, and the provision of a written informed consent. They could have been treated previously with 5-FU. In addition, at least 4 weeks had to have elapsed since the last chemotherapy administration. Patients with uncontrolled leptomeningeal or brain metastases, a second malignancy other than nonmelanoma skin carcinoma or carcinoma *in situ* of the cervix, extensive radiotherapy within the previous 4 weeks, uncontrolled comorbid illness and/or active infections were ineligible. Patients were excluded if they had chronic diarrhea, unresolved bowel obstruction, malabsorption syndrome, or inability to take oral medication. This study protocol was reviewed and approved by the Gil Medical Center (Incheon, Korea) institutional review board.

Treatment

Patients received two oral doses of S-1 40 mg/m^2, as an intermittent regimen of 4 weeks of treatment followed by a 2-week rest. Specifically, patients with a body-surface area (BSA) of less than 1.25 m^2 received 80 mg/day; those with a BSA of 1.25 m^2 or more but less than 1.5 m^2 received 100 mg/day; and those with a BSA ≥ 1.5 m^2 received 120 mg/day of S-1. When a grade ≥ 3 hematologic or grade ≥ 2 nonhematologic toxicity occurred, the temporary discontinuation of the S-1 administration was allowed until the toxicity subsided to grade ≤ 1. If grade ≥ 3 toxicity, which was likely related to S-1, was recorded, the subsequent dose of S-1 was reduced from 120 to 100, 100 to 80, 80 to 50, or 50 to 40 mg. If a rest period of 3 weeks or more was required or the daily dose of S-1 was reduced to below 40 mg, the patient was withdrawn from the study. Patients maintained a daily diary to record their intake of S-1 and any symptoms they experienced. MMC intravenous bolus at a dose of 7 mg/m^2 was given on day 1 in the first 4 cycles. MMC has a cumulative toxicity in the form of delayed thrombocytopenia and anemia, occasionally leading to hemolytic uremic syndrome [15]. To prevent the development of hemolytic uremic syndrome, the dose of MMC was restricted to a cumulative dose of 28 mg/m^2 [16]. MMC dose was reduced if grade ≥ 3 hematologic toxicity appeared. MMC was stopped if there was evidence of hemolytic anemia, severe and prolonged thrombocytopenia, or red cell fragmentation on peripheral blood smear. Treatment was repeated every 6 weeks. Patients without disease progression at the end of the fourth cycle could receive further courses of S-1 monotherapy.

Evaluation

Patients were evaluated for response if they received ≥ 1 cycle of treatment. If there was no disease progression after the first cycle, at least two cycles were administered. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumours [17] and was assessed by abdominopelvic computed tomography scan and by the same tests used initially to stage the tumor. Responses were confirmed at least 4 weeks later and reviewed by an independent investigator later at the time of analyses. Toxicity grading was based on the National Cancer Institute (NCI-CTCAE version 3) criteria.

Statistical considerations

The primary objective of this study was to determine the response rate of MMC plus S-1 in AGC. According to Fleming's single-stage method [18], at least 40 eligible patients were required on the basis of a test of a null hypothesis of a 10% response rate vs. an alternative of 25% (80% power and $P < 0.05$). Survival was calculated by the Kaplan–Meier method. All analyses were performed on an intent-to-treat basis provided that the main inclusion criteria were satisfied.

Results

Between October 2004 and May 2006, 43 eligible patients entered the study (Table 1). One patient did not receive protocol therapy because the patient died of massive hematemesis before the start of chemotherapy. Twenty-one percent of patients had an ECOG performance status of 2. Most common sites of metastatic disease were intra-abdominal lymph nodes (91%), peritoneum (77%) and liver (37%). A majority of patients (93%) were treated with 5-FU in their previous chemotherapy regimen. Twenty-six patients (61%) had received first-line chemotherapy with irinotecan-based regimen, six (14%) had received taxanes (paclitaxel or docetaxel), and three patients had received anthracycline-based chemotherapy. Twenty-three patients (54%) experienced an objective response to these first-line treatments.

Safety

A total of 121 chemotherapy cycles were delivered with a median of 2 per patient (range: 1–6). Treatment was

Table 1 Patient characteristics (*N*=43)

	No. of patients	%
Age, years		
Median (range)	53 (31–75)	
Sex, male	30	70
ECOG performance status		
0	13	30
1	21	49
2	9	21
Metastatic site (s)[a]		
Abdominal lymph node	39	91
Peritoneum	33	77
Liver	16	37
Lung and/or malignant pleural effusion	5	12
Bone	6	14
Supraclavicular lymph node	3	7
Ovary	3	7
First-line chemotherapy		
Irinotecan and leucovorin/5-FU	14	33
Irinotecan, leucovorin/5-FU, and cisplatin	11	26
Taxane (paclitaxel or docetaxel) and 5-FU	6	14
5-FU and cisplatin	5	12
5-FU protracted infusion	3	7
Epirubicin, cisplatin, and 5-FU	3	7
Irinotecan and cisplatin	1	2
Best response to first-line chemotherapy		
Complete/partial response	23	54
Stable disease	7	16
Progressive disease	12	28

ECOG, Eastern Cooperative Oncology Group; 5-FU, 5-fluorouracil.
[a]As patients could have metastases at multiple sites, the total number of metastases are greater than the number of patients.

discontinued during or after the first cycle of chemotherapy in 10 patients because of early progression of disease (eight patients), treatment refusal (one patient) and death (one patient). MMC dose was unchanged throughout the study, but discontinuation was required in two patients. Dose reduction of S-1 was required in 10 (24%) patients and affected 10 (8%) cycles. All eligible patients were evaluable for toxic effects (Table 2). The most frequently encountered toxic effects were gastrointestinal toxicities and fatigue, which were managed with rest, dose reduction, or treatment discontinuation. Even if all patients were pretreated with cytotoxic chemotherapy, only one episode of febrile neutropenia occurred. One patient developed hemolytic anemia after the first cycle of therapy, which was recovered with continuing S-1 monotherapy. Although difficult to differentiate from the symptoms of the underlying disease, one patient died of massive hematemesis during the first cycle. Two patients received platelet transfusion during the treatment. Grade ≥ 2 hand–foot syndrome was observed in only three patients.

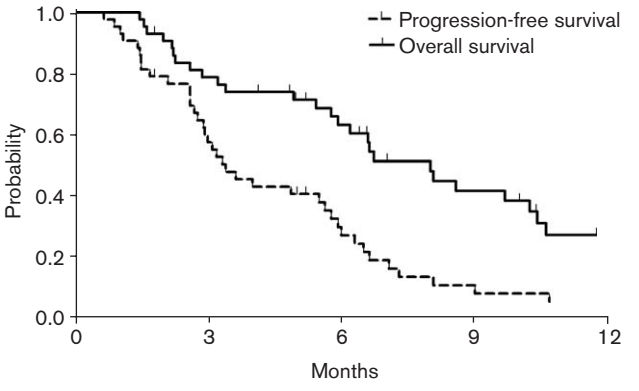
Efficacy

Ten patients out of a total of 43 patients, who discontinued their treatment before the start of second cycle, were considered as nonresponders in an intent-to-treat analysis. We obtained one complete and eight partial responses [overall response rate 21%, 95% confidence interval (CI): 9–34%], which maintained for a median of 4.1 months (95% CI: 2.5–5.8 months). All clinical responses occurred between 64 and 98 days after the initiation of treatment. Of the nine responding patients, eight had been previously treated with a 5-FU-based combination. In nine patients (21%) the disease remained stable. With a median follow-up of 13 months, the median progression-free survival was 3.4 months (95% CI: 2.3–4.5 months), failure-free survival was 3.3 months (95% CI: 2.9–3.8 months) and the overall survival time was 8.0 months (95% CI: 6.1–9.9 months), as shown in Fig. 1. No relationship between response rate or overall survival and previous chemotherapy regimen or previous response to treatment was noted. Only one of the eight patients who had an ECOG performance status of 2, however, responded to the second-line regimen of this study. Patients with an ECOG performance status of 0 or 1 achieved an overall response rate of 24%. The overall survival was significantly higher in patients with an ECOG performance status of 0 or 1 (8.1 months) than those with ECOG 2 (2.6 months, $P = 0.016$). Multivariate analysis revealed that only ECOG performance status (0 or 1 vs. 2) had a significant effect on the hazard of death (hazard ratio: 0.35, 95% CI: 0.14–0.86).

Table 2 Maximum grade toxicity per patient (*N*=42)

	Grade 1–2		Grade 3–4	
	N	%	*N*	%
Anemia	8	19	3	7
Neutropenia	4	10	2	5
Thrombocytopenia	1	2	2	5
Nausea and vomiting	8	19	3	7
Anorexia	5	12	2	5
Stomatitis	6	14	4	10
Diarrhea	10	24	4	10
Fatigue	8	19	5	12
Peripheral neuropathy	2	5	0	
Hepatic	2	5	0	
Renal	2	5	0	
Dermatologic	3	7	2	5

Fig. 1



Progression-free and overall survival.

Discussion

AGC is an incurable condition where the aim of treatment is to improve survival and to palliate symptoms. Disease may respond to several types of chemotherapy initially, and these treatments have been shown to provide palliation as indicated by improvement in duration and/or quality of survival [2,3]. When patients do not respond to chemotherapy or eventually develop disease progression, however, no established second-line therapy can be offered. No evidence exists that second-line chemotherapy in patients with AGC will result in substantial prolongation of survival. Moreover, there is potential for toxicity from the treatment. Despite favorable outcomes seen in some phase II trials of second-line chemotherapy for AGC [19–23], the results from phase II trials may not be generalized to the routine clinical situation. Eligibility criteria tend to result in the recruitment of a relatively good prognostic group.

Currently, the availability of a number of new drugs with a favorable toxicity profile, and their nonoverlapping mechanisms of action, has provided opportunities to reevaluate the role of second-line treatment in patients with AGC. Oral chemotherapy has the advantage of greater patient convenience and acceptance with potential cost saving [24]. In general, second-line treatment in AGC should be used to prolong survival and improve the quality of life of the patients. These goals should be met through the use of well-tolerated regimens with a reasonably convenient administration scheme to avoid frequent visits to the clinic. In a recent report, we focused on the quality of life issues and demonstrated that second-line chemotherapy may be of value [25].

The rationale for combining MMC with fluoropyrimidine was based on the different mechanisms of cytotoxic action of the drugs, the potential for improved antitumor activity, and their nonoverlapping adverse effects. In human colon cancer cell lines, the combination of MMC and 5-FU was synergistic [10]. MMC has been used in combination with 5-FU to treat gastrointestinal cancers [12,13,16]. MMC plus FT-uracil, another oral fluoropyrimidine that contains tegafur and uracil, demonstrated no significant survival benefit compared with 5-FU [26]. Koizumi *et al.* [27] treated AGC patients with oral 5′-deoxy-5-fluorouridine, an intermediate of capecitabine, with or without MMC. Response rates and overall survival were greater in patients who received MMC but were not statistically significant. Toxicity profiles were similar.

The main toxicity of the MMC and S-1 combination in this study was gastrointestinal toxicities and fatigue. Severe hematologic toxicities were infrequent and febrile neutropenia occurred in only one patient. Hemolytic anemia was suspected in one patient, whereas grade 3 or 4 thrombocytopenia occurred in two patients. These results suggest that the toxicity profile of this combination chemotherapy is not significantly different from that reported in chemotherapy-naive AGC patients treated with S-1 monotherapy [5,28]. A possible explanation for such favorable toxicity profile may rest on the relatively young age of the study patients (median age: 53 years), the lower cumulative MMC dosage used in our study, and the nonoverlapping toxicities of S-1 and MMC, characterized by gastrointestinal symptoms and delayed thrombocytopenia. This favorable toxicity profile of the regimen is of importance, as the primary objective of second-line treatment in AGC patients is palliative in nature. Although 21% objective tumor responses, accompanied with a median survival of 8 months, did not reach the predefined therapeutic goal (> 25%), it is interesting to note that the results compared favorably with results of earlier studies involving patients who received second-line chemotherapy for AGC [29]. Although the results presented here are from a relatively small, single-arm phase II study, the results suggest that the addition of MMC could improve efficacy of S-1 without compromising safety. In contrast, patients with poor performance status (i.e. ECOG 2) rarely respond to second-line therapy. The disappointing efficacy results in these patients indicate that second-line chemotherapy in patients with poor performance status should be given with caution and consideration should be warranted to exclude such patients from future clinical trials.

Patients who had been previously treated with 5-FU-containing chemotherapy were considered eligible in this study. One may argue that it is more prudent to avoid fluoropyrimidines in salvage regimen for these patients. 5-FU, however, remains the backbone for most of the current chemotherapy protocols for AGC while the treatment options have expanded in recent years to include newer agents [4,8,11]. It may not be practical to exclude patients who received 5-FU in their first-line chemotherapy. We found no significant relationship between response rate or overall survival and previous chemotherapy regimens. It should be kept in mind that it represents only a small group of patients with AGC in this phase II study. Caution is also required so that our results are not misinterpreted as superiority of S-1 over other oral fluoropyrimidines.

In conclusion, the low incidence of toxicities associated with the activity of MMC plus S-1 combination is of particular relevance because it suggests that the regimen could be used in patients with an ECOG performance status of 0 or 1 who cannot tolerate aggressive combination chemotherapy. Further studies are warranted to evaluate this regimen if proven to have an additional value in first-line setting.

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