

# A phase II trial of 5-fluorouracil, leucovorin and mitomycin C in patients with advanced gastric cancer

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## ABSTRACT

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**Aims and background.** Low-dose leucovorin is a well known potentiator of 5-fluorouracil activity in colorectal cancer but not in gastric cancer. To assess their efficacy on response rate and survival, 5-fluorouracil and low-dose leucovorin were combined with mitomycin C.

**Methods.** Fifty patients with gastric cancer and metastatic disease, unresectable or relapsed disease were treated with the following regimen every 28 days: mitomycin C, 7 mg/m<sup>2</sup> IV bolus on day 1, and leucovorin, 20 mg/m<sup>2</sup> IV, followed immediately by 5-fluorouracil, 375 mg/m<sup>2</sup> on days 1-5. All had measurable disease and were assessable for toxicity. Prognostic factors were analyzed to examine any association with response rate or overall survival.

**Results.** Nineteen of the 48 assessable patients (39.6%; 95% confidence interval [CI], 25.8-53.4) responded, including 4 complete responses (8.3%). The median progression-free survival was 108 days (range, 18<sup>+</sup> - 146), and the median duration of survival was 338 days (11.3 months; range, 18<sup>+</sup> - 903 days). Response rate and overall survival were not significantly associated with CEA level, performance status, age, or primary and metastatic tumor sites. Toxicity associated with the chemotherapy was tolerable, and all patients were treated at the outpatient clinic. Leukopenia and thrombocytopenia WHO grade  $\geq 3$  occurred in 5% and 1% of the patients, respectively. Nausea and vomiting were the most frequent adverse effects (29%), all grade 1 or 2.

**Conclusions.** Combination chemotherapy of 5-fluorouracil plus leucovorin with mitomycin C is effective for the treatment of advanced gastric cancer and is well tolerated.

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## Introduction

Gastric cancer is one of the leading causes of death from cancer worldwide, especially in Korea, where it is the third most frequent cause of cancer-related deaths<sup>1</sup>. 5-fluorouracil (5-FU)/cisplatin combination has long been a reference regimen for the treatment of advanced gastric cancer in Korea, but it has not been successful in substantially improving overall survival<sup>2-5</sup>. In addition, associated toxicities are often severe; anorexia and nausea/vomiting are significant toxicities in cisplatin-containing regimens<sup>2-5</sup>. Recently, although several studies had announced the equivalent or better efficacy for the treatment of advanced gastric cancer with a newer regimen including oxaliplatin<sup>6-10</sup>, the cisplatin-containing regimen is still widely used in practice.

5-FU and leucovorin (LV) have been used in colorectal cancer chemotherapy, with fair toxicity profiles and convenient administration. However, the optimal route of administration and dose of 5-FU/LV have not yet been determined; low-dose LV has been shown to be as effective as high-dose treatment in some studies<sup>11,12</sup>.

Several studies have shown that 5-FU plus high dose LV-based chemotherapy is effective for the treatment of advanced gastric cancer<sup>13-16</sup>. However, low-dose LV has not been extensively evaluated for its efficacy in advanced gastric cancer. Mitomycin

**Key words:** 5-fluorouracil, advanced gastric cancer, leucovorin, mitomycin C, overall survival, response.

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C (MMC) is an active drug for gastric cancer treatment<sup>17-20</sup>. A pilot study in our hospital showed encouraging results using MMC, 5-FU and low-dose LV<sup>21</sup>.

The goal of this trial was to determine the antitumor activity and toxicity of 5-FU, low-dose LV and MMC combination chemotherapy for the treatment of patients with advanced gastric carcinoma.

## Patients and methods

### Eligibility

Patients with histologically confirmed unresectable, relapsed or metastatic adenocarcinoma of the stomach were enrolled for the study. Eligibility criteria included at least one measurable lesion (defined as a mass with clearly demarcated dimensions on computed tomography, routine chest X-ray or physical examination), no prior adjuvant chemotherapy at least within one year before enrollment, an Eastern Cooperative Oncology Group performance status of 3 or better, age older than 15 years, life expectancy longer than 4 weeks, no concurrent uncontrolled medical illness, no other malignancies (with the exception of squamous cell carcinoma of the skin treated by surgery), and adequate renal, hepatic and bone marrow function (serum creatinine  $\leq 2$  mg/dL, total bilirubin  $\leq 3$  mg/dL, granulocyte  $\geq 1,800/\mu\text{L}$  and platelets  $\geq 100,000/\mu\text{L}$ ). A complete history and physical examination were performed on all patients. Initial assessment included the carcinoembryonic antigen (CEA) test, electrocardiography, radiologic evaluation with chest X-ray and abdominal CT scan, and gastrofiberscopy with biopsy. A signed informed consent was obtained from all patients for study participation.

### Treatment

Patients received MMC, 7 mg/m<sup>2</sup> IV bolus on day 1, 5-FU, 375 mg/m<sup>2</sup> IV over 15 min, immediately preceded by LV, 20 mg/m<sup>2</sup> IV bolus on days 1 through 5 every 4 weeks. In the event of toxicity, the following dose reductions and treatment delays were planned. When the nadir of the hematological toxicity was at WHO grade IV (ANC  $< 500/\mu\text{L}$  and/or platelet  $< 25,000/\mu\text{L}$ ), MMC was reduced to 5 mg/m<sup>2</sup> and 5-FU/LV to 4 days from the next cycles. When the granulocyte count was between 1,000 and 1,799/ $\mu\text{L}$  and/or the platelet count between 75,000 and 99,999/ $\mu\text{L}$ , 5-FU and LV were given for 4 days and MMC at 5 mg/m<sup>2</sup>. If the granulocyte and/or platelet counts were below 1,000/ $\mu\text{L}$  and 75,000/ $\mu\text{L}$  respectively, the treatment was delayed for up to 14 days. If recovery did not occur at this point, the treatment was discontinued. The complete blood cell counts (CBC) were checked between days 8-15 and whenever necessary to monitor the nadir blood cell counts thereafter. For grade 3 stomatitis or diarrhea, 5-FU/LV was given for 4 days, and the treatment was discontinued for grade 4

toxicity. Serum creatinine, liver enzymes, CBC and electrolytes were assessed before each treatment cycle.

### Response and toxicity evaluation

Response assessment according to the physical examination and chest X-ray was performed before every cycle. An abdominal CT scan or ultrasound was repeated before every 2 cycles of chemotherapy or any time disease progression was suspected. Blood chemistry, CBC and CEA were evaluated before every cycle. Response and toxicity were classified according to WHO criteria<sup>22</sup>. Toxicity was evaluated before each cycle of therapy.

A complete response (CR) was defined as the disappearance of all measurable or assessable disease, signs, symptoms and biochemical changes related to the tumor for at least 4 weeks. A partial response (PR) was defined as a reduction of 50% or more in the sum of the products of the perpendicular diameter of all measured lesions lasting  $\geq 4$  weeks. Stable disease (SD) was defined as a less than 50% reduction and less than 25% increase in the sum of the products of two perpendicular diameters of all measurable lesions without the appearance of new lesions. Progressive disease (PD) was defined as the appearance of any new lesion or definite increase in tumor size, and more than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions. Treatment was continued until tumor progression or unacceptable toxicity occurred.

### Statistics

Based on previous results of 5-FU plus MMC in advanced gastric cancer<sup>17,23</sup>, we hypothesized 35% as an expected response rate and 20% as a minimal acceptable response rate. Using the Simon two-stage phase II design (Minimax Design) and considering a drop-out rate of 5% with  $\alpha$ -error and  $\beta$ -error at 0.10 and 0.10, respectively, the minimum number of patients needed was 48. If response was seen in less than 6 patients out of the first 33 on interim analysis, the study was planned to be stopped.

Progression-free survival was calculated from the date of beginning of treatment to the date of disease progression or any cause of death. Overall survival was calculated from the date of beginning of treatment to the date of death from any cause. All statistical analyses were performed using SPSS for Windows version 14.0 (SPSS Inc., Chicago, IL, USA). Proportions and categorical data were compared using Fisher's exact test. Survival curves were analyzed by the Kaplan-Meier method. All analyses were two-sided, and statistical significance was defined when  $P < 0.05$ . The primary objective was to examine the response rate and toxicity. The secondary objectives were to examine the progression-free and overall survival.

**Results**

*Patient characteristics*

Fifty patients were enrolled in the study and could be evaluated; two patients were lost to follow-up. The patient characteristics are listed in Table 1. The median patient age was 57 (range, 24-72); 29 patients were male (58.0%) and 21 female (42.0%). Most of the patients were in good general condition (71.4% with a performance status 0 or 1). All patients had histologically confirmed adenocarcinoma.

Seven of 50 patients had undergone surgery previously. Out of 7, 3 underwent surgery only and 4 underwent surgery followed by 5-FU-based adjuvant chemotherapy. The common metastatic sites were the liver and distant lymph nodes (20 patients [46.5%] each).

*Response to chemotherapy*

Forty-eight of 50 enrolled patients were assessable for antitumor activity. The best responses are shown in Table 2. Four (8.3%) patients had CR and 15 (31.3%) had PR, for an overall best response rate of 39.6% (95% confidence interval (CI), 25.8-53.4). Thirteen patients (27.1%) had SD. Including 2 patients lost to follow up, the median progression-free survival was 108 days (range, 18<sup>+</sup> -146) (Figure 1), and median overall survival was 338 days (11.3 months; range, 18<sup>+</sup> - 903) (Figure 2). After disease progression, 10 patients received second-

**Table 1 - Patient characteristics**

|   | No.      | %         |
|---|----------|-----------|
| No. of patients                                   | 50       | 100       |
| Lost to follow-up                                 | 2        | 4         |
| Assessable  | 48       | 96        |
| Sex (Male/Female)                                 | 29/21    | 58.0/42.0 |
| Age, years  |          |           |
| Median  | 57       |           |
| Range   | 24-72    |           |
| Performance status (ECOG); 42 patients assessable |          |           |
| 0   | 1        | 2.4       |
| 1   | 29       | 69.0      |
| 2   | 10       | 23.8      |
| 3   | 2        | 4.8       |
| Tumor status                                      |          |           |
| Stage IV  | 43       | 86.0      |
| Recurred after surgery only                       | 3        | 6.0       |
| Recurred after adjuvant CT                        | 4        | 8.0       |
| Primary site                                      |          |           |
| Antrum  | 25       | 50.0      |
| Other   | 25       | 50.0      |
| Metastatic sites                                  |          |           |
| Liver   | 20       | 46.5      |
| Lung  | 3        | 7.0       |
| Bone  | 3        | 7.0       |
| Peritoneum  | 7        | 16.3      |
| Ovary   | 4        | 9.3       |
| Lymph node only                                   | 20       | 46.5      |
| No. of treatments (median)                        | 1-14 (4) |           |

**Table 2 - Best responses**

|                     | No. of patients    | % of assessable patients (n = 48) |
|---------------------|--------------------|-----------------------------------|
| NA                  | 2                  |                                   |
| Complete response   | 4                  | 8.3                               |
| Partial response    | 15                 | 31.3                              |
| Stable disease      | 13                 | 27.1                              |
| Progressive disease | 16                 | 33.3                              |
| ORR (95% CI)        | 39.6 (25.8 – 53.4) |                                   |

NA, not assessable; ORR, overall response rate; CI, confidence interval.

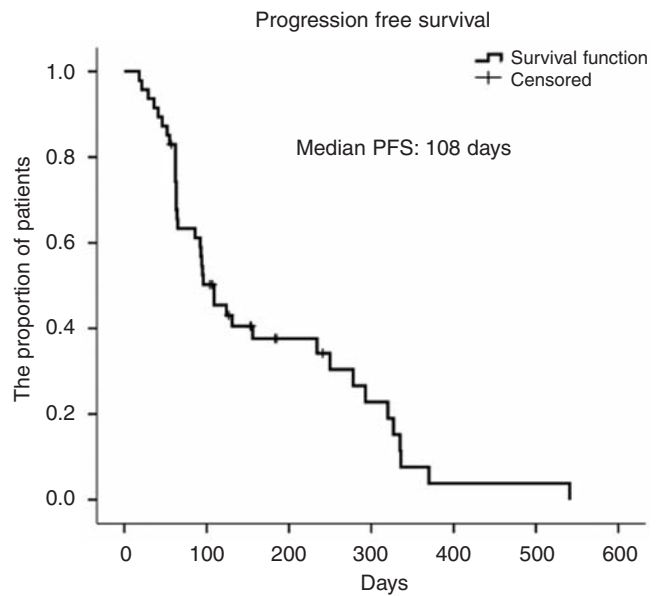


Figure 1 - Progression free survival (median 108 days; range, 18<sup>+</sup> - 146 days).

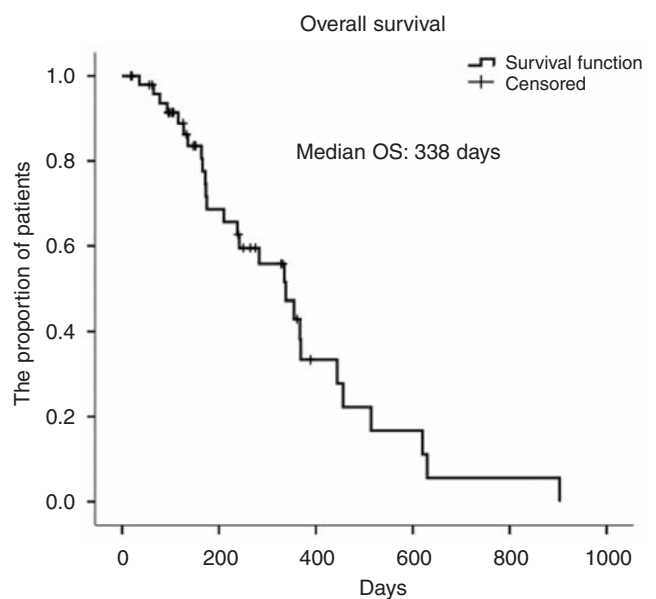


Figure 2 - Overall survival (median 338 days; range, 18<sup>+</sup> - 903 days).

line chemotherapy. 5-FU/LV was introduced in 4 patients, 5-FU/cisplatin in 3 patients, docetaxel/oxaliplatin in 2 patients, and etoposide/doxorubicin/cisplatin in 1 patient. No patient received more than 3 cycles of second-line chemotherapy.

#### Prognostic factor analysis

The analysis of a few parameters that might be related to prognosis is shown in Table 3. The response rate and overall survival were not significantly associated with CEA level, performance status, age, or primary and metastatic tumor sites.

#### Safety

A total of 224 cycles of chemotherapy (median, 4, range, 1-14) were analyzed in the 50 eligible patients. Toxicities experienced during treatment are listed in Table 4. In general, the chemotherapy was tolerable. Leukopenia, neutropenia and thrombocytopenia, WHO grade 3-4, were present in 5%, 14% and 1% of the patients, respectively. Nausea/vomiting was the most frequent adverse effect (29%), all in patients with grade 1 or 2 toxicity. No patient had neutropenic fever or treatment-related death. No patient developed microangiopathic hemolytic anemia or hemolytic uremic syndrome during the chemotherapy and observation period.

#### Discussion

This study was performed to identify a treatment protocol easy to administer with good patient outcomes for Korean patients with advanced gastric cancer. The results of the study suggest that chemotherapy with 5-FU/low-dose LV plus MMC is convenient to administer and well tolerated as first-line therapy in the outpatient clinic.

**Table 3 - Prognostic factor analysis**

|                    | Response rate | P    | Median survival (days) | P    |
|--------------------|---------------|------|------------------------|------|
| Serum CEA level    |               |      |                        |      |
| >10 µg/L           | 47.4          | 0.12 | 335                    | 0.06 |
| ≤10 µg/L           | 23.8          |      | 456                    |      |
| Performance status |               |      |                        |      |
| 0, 1               | 28.6          | 0.42 | 355                    | 0.53 |
| 2, 3               | 41.7          |      | 335                    |      |
| Age                |               |      |                        |      |
| >60                | 38.1          | 0.30 | 444                    | 0.48 |
| ≤60                | 37.9          |      | 335                    |      |
| Primary sites      |               |      |                        |      |
| Antrum             | 25.0          | 0.30 | 335                    | 0.94 |
| Other sites        | 42.3          |      | 338                    |      |
| Metastatic sites   |               |      |                        |      |
| Viscera            | 40.0          | 0.72 | 338                    | 0.51 |
| Lymph node only    | 35.0          |      | 367                    |      |

**Table 4 - Toxicities (WHO grade)**

| Hematologic toxicities (224 cycles)                         |     |    |    |    |   |
|---|-----|----|----|----|---|
| Grade   | 0   | 1  | 2  | 3  | 4 |
| Leukopenia  | 145 | 51 | 23 | 5  | 0 |
| Neutropenia   | 152 | 31 | 27 | 12 | 2 |
| Thrombocytopenia  | 213 | 4  | 4  | 2  | 1 |
| Non-hematologic toxicities (50 patients: worst per patient) |     |    |    |    |   |
| Grade   | 0   | 1  | 2  | 3  | 4 |
| Nausea/Vomiting   | 43  | 6  | 1  | 0  | 0 |
| Diarrhea  | 48  | 0  | 2  | 0  | 0 |
| Stomatitis  | 47  | 2  | 1  | 0  | 0 |

The overall response rate of 39.6%, with a complete response in 8.3%, and median overall survival of 11.3 months are similar to the range reported in phase II studies with various combinations of 5-FU, doxorubicin, high-dose methotrexate, etoposide and cisplatin<sup>24,25</sup>, and more recent studies with taxane-, oxaliplatin- or irinotecan-based regimens, all of which have shown overall response rates of 30% to 70% and CR rates of 5% to 10%<sup>4-7,9,26,27</sup>, which compared favorably with the results of the present study, which included some patients with a performance status of 3 and 70 years or older.

There have been many trials on treatments for advanced gastric cancer with regimens including 5-FU/LV, since it was proven to be active against colorectal cancer. The optimal dose of LV has not been determined for the treatment of gastric cancer. High-dose LV in the range of 100-500 mg/m<sup>2</sup> has been combined with 5-FU in several studies. The combinations of etoposide, 5-FU and high-dose LV have been reported to have response rates of 27-39% and a median survival of 8-10 months in weak or elderly patients<sup>15,28</sup>. MMC with high-dose LV and 5-FU yielded a response in 4 of 7 patients in a pilot study<sup>13</sup>.

Poon *et al.*<sup>11</sup> used 5-FU with low-dose LV at 20 mg/m<sup>2</sup> for the treatment of colorectal cancer and obtained a survival advantage similar to 5-FU with high-dose LV. In the treatment of gastric cancer, there have been several trials of LV at 20 mg/m<sup>2</sup> and 5-FU with one or two drugs, including irinotecan, paclitaxel, epirubicin, oxaliplatin and cisplatin, resulting in a response rate of 10-46% and overall survival of 10-14 months<sup>26,29-31</sup>, which are not inferior to the results with high-dose LV<sup>6,8,10,32-39</sup>. The results of this study also demonstrated that low-dose LV-based combination treatment was active against gastric cancer.

In our study, 5-FU was administered as bolus for the convenience of a rapid drug administration instead of continuous infusion, which usually requires a central venous line. In the light of previous reports on the direct comparison of 5-FU continuous infusion and 5-FU/LV

bolus<sup>40,41</sup>, there seems to be no significant difference in terms of overall survival.

The toxicity of the regimen was mild; the most significant hematological toxicity, grade 3-4 neutropenia, was observed in only 14% of all patients, with no non-hematological toxicity of grade 3 or 4, even in patients at an advanced age and/or with a poor performance. Although it is difficult to compare toxicity with other studies, the toxicities observed in our study were much less than those reported with 5-FU/cisplatin combinations<sup>2-5</sup>. No patient developed microangiopathic hemolytic anemia or hemolytic uremic syndrome with the use of mitomycin C. This might in part be due to the low dose of the drug used in the study. All of the patients were given chemotherapy on an outpatient basis. This, as well as the lower cost of low-dose LV, provides improved cost effectiveness and convenience.

Several possible prognostic factors such as serum CEA, performance status, age, primary and metastatic sites were not associated with the response rate or survival of the patients in the study. These results differ from other studies where age, performance status<sup>42</sup> and lymph node metastasis<sup>43</sup> were important prognostic factors. The reason for this difference is not clear, but the study is too small to provide conclusive evidence.

In conclusion, the combination of mitomycin C, 5-FU and LV is safe and has activity comparable with current regimens including taxane or oxaliplatin. The regimen is convenient to administer in the outpatient department, and it has a lower cost. It may be attractive to patients with an advanced age and/or a poor performance status who may not be able to tolerate more intensive chemotherapeutic agents, such as cisplatin.

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