Mitomycin C (MMC) with Weekly 24-Hour Infusions of High-Dose 5-Fluorouracil and Leucovorin in Patients with Advanced Gastric Cancer

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Background: We have reported a 33% response rate with 5-fluorouracil/leucovorin (5-FU/LV) treatment along with a median survival of 7 months in patients with advanced gastric cancer. Subsequently, mitomycin C (MMC) became our target agent for the combination because of its activity towards gastric cancer.

Methods: From May 1998 to December 2000, a total of 37 chemo-naive patients with advanced gastric cancer were included. There were 20 men and 17 women with a median age of 58 (range, 21-73) years. The regimen consisted of 2600 mg/m^2 5-FU and 100 mg/m^2 LV admixed in an outpatient infusion pump administered for 24 hours every week for 6 weeks, followed by a 2-week break; then 10 mg/m^2 MMC was given once every 8 weeks. The treatment continued until disease progression or unacceptable toxicity was noted, or the patient refused.

Results: In total, 404 treatments of 5-FU/LV were given. The mean number of treatments was 10 (range, 1 to 24). The intent to treat response rate was 40.5% (15/37) with 5.4% (2/37) showing a complete response. The median time to disease progression was 4.5 months. The median survival time was 8.0 months. All of the patients were evaluated for toxicity. Less than 10% of the patients developed grade III/IV toxicity.

Conclusion: MMC with weekly 24-hour infusions of high-dose 5-FU and LV produced moderate activity in patients with advanced gastric cancer, and patients showed acceptable toxicity.

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Key words: **gastric cancer, mitomycin C, 5-fluorouracil, leucovorin.**

Gastric adenocarcinoma remains one of the leading causes of cancer deaths worldwide, with a current 5-year survival of less than 20%.[1,2] Approximately 25% of patients with gastric cancer are associated with disseminated disease at presentation, and more than 1/2 of patients with localized disease experience recurrence within 5 years.[3-6] Systemic chemotherapy is widely used in patients with advanced gastric cancer, since it is relatively sensitive to chemotherapy. Randomized trials versus best supportive care have also shown significant gains in median survival using polychemotherapy

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(from 3 months to 10 months), thus establishing the palliative role of chemotherapy in advanced states.[7,8] 5-Fluorouracil (5-FU)-based regimens, used either alone or in combination with other drugs, are commonly used in general clinical practice. The treatment yields only 20%-50% response rates with very few complete responses.[6-11]

Several preclinical studies have suggested that the biochemical modulation of 5-FU infusion by leucovorin (LV) can enhance antitumor activities. Clinical controlled trials have confirmed the increase in objective response rates in patients with metastatic colorectal cancer treated with a 5-FU infusion and LV compared with those treated with a 5-FU infusion alone or with a 5-FU bolus and LV.[12,13] Weekly 24-hour infusions of high dose 5-FU (2600 mg/m^2) and LV in patients with advanced colon cancer have been reported.[14] Vanhoefer et al.[15] and Hsu et al.[16] showed that weekly 24-hour infusions of high-dose 5-FU (2600 mg/m^2) and LV had response rates of 18% and 48% for patients with gastric cancer, respectively. We reported on a prospective study using a similar regimen on chemo-naive patients with advanced gastric cancer in 1999,[17] for which the response rate was 33%, and the overall median survival was 7 months. The adverse effects were minimal. However, we did not observe a complete response in the previous series, and there were no obvious differences in the median survival compared to other 5-FU-based regimens. Adding other active agents for patients with advanced gastric cancer in order to improve the response and survival was warranted. Subsequently, we added bimonthly cisplatin (CDDP) into weekly 24-hour infusionsof high-dose 5-FU and LV. The response rate was slightly higher, but toxicities were higher than that of the weekly 24-hour infusions of high-dose 5-FU and LV.[18] Mitomycin C (MMC) has been reported to be one of the most active agents against gastric cancer.[19] Objective responses of approximately 30% were reported in 211 patients with gastric cancer when it was given as a single agent.[20,21] Clinical synergy between MMC and a 5-FU infusion in colorectal cancer was reported by Ross et al.[22] In addition, Grumett et al.[23] showed that MMC with high-dose 5-FU/LV produced activity in patients with advanced colorectal cancer resistant to 5-FU/LV. Therefore, we applied MMC to our weekly 24-hour infusions of high-dose 5-FU with LV to evaluate the response rates and toxicity. Herein, we report our experiences with MMC and weekly 24-hour infusions of 5-FU/LV.

METHODS

Only patients who had primary gastric cancer known to be beyond the hope of cure, that is, histologic proof of residual primary, recurrent, or metastatic disease were enrolled. Tumors had to be radiologically measurable or evaluable. Only patients who had had no prior chemotherapy and whose Eastern Cooperative Oncology Group (ECOG) performance status was ≤ 2, absolute granulocyte count was ≥ 1500/ml, platelet count was ≥ 100,000/ml, serum creatinine concentration was ≤ 2 mg/dL, and serum bilirubin was ≤ 3.0 mg/dL were accepted into the study.

Each patient received a central vascular device through a subclavian vein for outpatient infusion therapy. The chemotherapy consisted of 2600 mg/m^2 5-FU and 100 mg/m^2 LV admixed in an outpatient infusion pump administered for 24 hours every week for 6 weeks, followed by a 2-week break, after which 10 mg/m^2 MMC was given once every 8 weeks. However, if grade 3 hematological or gastrointestinal toxicity according to the WHO Toxicity Guidelines was observed, the dose of 5-FU was reduced to 2000 mg/m^2. The chemotherapy was repeated every 8 weeks with a 2-week break until disease progression or unacceptable toxicity was noted, or the patient refused.

Prior to therapy, each patient was evaluated using a complete history review, physical examination, complete blood counts, biochemical profile, serum tumor marker, chest roentgenogram, and abdominal computed tomographic scan (CT scan). Patients were reassessed after 8 weeks using the same procedures. When suggested disease progression during treatment was found, an evaluation was immediately performed. A complete response (CR) was defined as disappearance of all measurable disease based on imaging studies. A partial response (PR) was defined as a 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions, or a decrease of at least 50% of 1 dimension of evaluable lesions for at least 4 weeks without the appearance of new lesions. Stable disease (SD) was defined as a

decrease in lesions for at least 4 weeks, which did not reach the criteria of PR, or a less than 25% increase in lesions. Progressive disease (PD) was defined as a 25% or greater increase in the size of 1 or more evaluable lesions, or the appearance of new lesions. The presence of ascites was not considered a criterion for measuring the response; however, the appearance of ascites was considered progression.

The time to progression was measured from the start of therapy to the date of progression or discontinuation from the study due to toxicity. The survival time was calculated from the start of therapy to the date of death, and was established using the Kaplan-Meier method.

RESULTS

From October 1998 through December 2000, treatment was administered to 37 consecutive patients. Patient characteristics are summarized in Table 1. There were 20 men and 17 women, with a median age of 58 (range, 21 to 73) years. The sites of disease involvement included the local-regional area (34), peritoneum (14), liver (13), intra-abdominal lymph nodes (8), extra-abdominal lymph nodes (6), lung (1), bone (1), and others (5). In total, 404 chemotherapy treatments were given with a mean of 10 (range, 1-24). Dose reduction was required for 7 patients (17.9%) due to side effects of the chemotherapy. All were reduced by 1 level of dosage. The majority of the chemotherapy was given at outpatient clinics.

Three patients were not included in the evaluation of tumor responses, 1 patient had a cerebrovascular accident, and 2 patients were lost to follow-up. Thus, these patients were classified as non-responders. Thirty-four patients were evaluated for responses. For the intent-to-treat analysis, the response rate was 40.5% (15/37) (95% confidence interval [C.I.], 24%-57%) with 2 (5.4%) complete responses. Nine patients (24.3%) had stable disease. The median time to progression was 4.5 months (95% C.I., 3.7-6.3 months). The overall median survival was 8 months (95% C.I., 6.8-10.2 months). The 2 complete responders survived for 36 and 34 months, respectively. The causes of death of the 2 complete responders were brain metastases and gastric cancer with bleeding, respectively.

The toxicity profiles are summarized in Table 2. Less than 10% of patients developed grade III/IV toxicity; 3 patients (8%) developed grade III neutropenia, 1 patient (3%) had grade IV thrombocytopenia, 5 patients (13%) suffered from grade III/IV vomiting, 2 (6%) patients exhibited diarrhea, 2 patients (6%) suffered from mucositis, and 3 patients (8%) had grade III fatigue. One patient was admitted to the hospital due to severe vomiting-induced hyponatremia. There were no treatment-related deaths. No pump-infusion or catheter-related complications were identified.

Table 1. Patient Characteristics

Characteristic	No. of patients
Gender: female/male (%)	17/20 (46/54)
Median age (years) (range)	58 (21-73)
Performance status (ECOG)	
0	1
1	24
2	12
Mean number of chemotherapy treatments (range)	10 (1-24)
Number of tumor involvement sites	
1	2
2	24
3	10
4	1
Tumor involvement sites	
Local-regional	34
Liver	13
Peritoneum	14
Intra-abdominal lymph nodes	8
Extra-abdominal lymph nodes	6
Lung	1
Bone	3
Others	5

Table 2. Maximal Toxicity (according to WHO criteria) (N=37)

	Toxicity				
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WBC	23 (62)	5 (14)	6 (16)	3 (8)	0
Platelets	28 (75)	5 (14)	3 (8)	0	1 (3)
Vomiting	22 (59)	5 (14)	5 (14)	3 (8)	2 (5)
Diarrhea	29 (78)	0	6 (16)	1 (3)	1 (3)
Mucositis	31 (83)	1 (3)	3 (8)	1 (3)	1 (3)
Skin	33 (90)	4 (11)	0	0	0
Fatigue	28 (76)	4 (11)	2 (5)	3 (8)	-
CNS	36 (97)	0	0	1 (3)	0
Hyponatremia	36 (97)	0	0	0	1 (3)

Percent in parenthesis

DISCUSSION

MMC has been reported to be one of the most active agents against gastric cancer.[19] Objective responses of approximately 30% were reported in 211 patients with gastric cancer when it was given as a single agent.[20,21] Our present study demonstrated that MMC and weekly 24-hour infusions of high-dose 5-FU and LV could achieve up to a 40.5% response rate, with a median survival of 8.0 months against advanced gastric cancer.

To the present, no regimen has been regarded as a standard treatment for patients with advanced gastric cancer. The EORTC presented a phase III randomized comparison study of FAMTX (5-FU, methotrexate, and doxorubicin), ELF (5-FU, LV, and etoposide), and PF (cisplatin and 5-FU).[24] The response rates of these regimens were less than 20%. The study showed no advantages of efficacy or survival among the 3 regimens. In addition, more than 30% of patients developed grade 3 or 4 neutropenia. Weekly 24-hour infusions of high-dose 5-FU and LV provide higher dose-intensities of 5-FU as compared to those with FMATX, ELF, and PF. The authors suggested that a combination regimen using weekly infusions based on high-dose 5-FU was a promising approach for the treatment of gastric cancer.[24,25]

In fact, weekly 24-hour infusions of high-dose 5-FU and LV for patients with advanced gastric cancer has been used since 1994 and has achieved moderate activity. However, both the optimal treatment dose (high-dose vs. low-dose folinic acid) and treatment schedule (sequential vs. mixed infusions of folinic acid and 5-FU) for the combination are yet undetermined. Vanhoefer et al.[15] reported this regimen as salvage chemotherapy for refractory advanced gastric cancer and achieved an 18% response. Hsu et al.[16] reported in their retrospective study that chemo-naive patients had a 48% response, and only 2.9% of patients developed grade 3 or 4 leukopenia or non-hematological toxicity. We used weekly 24-hour infusions of high-dose 5-FU and LV, and these produced a 33% response rate and 7 months for the median survival in 1999.[17] All of the reported toxicities were minimal. Based on these data, we consider our regimen to be simple to deliver and low in cost, and to have a similar response; therefore, we have continued to use this regimen as the basis to treat our gastric cancer patients.

Results of the present study are very similar to those reported by Kretzschmar et al.[26] The treatment dose schedule by Kretzschmar was 15 mg/m^2 MMC on day 1 of a 7-week cycle followed by a 2-hour infusion of 500 mg/m^2 folinic acid and a 24-hour infusion of 2600 mg/m^2 5-FU on days 1, 8, 15, 22, 29, and 36. They achieved a 37% response rate without a complete response, and the median survival was 7 months in 30 patients. The regimen in our study consisted of 10 mg/m^2 MMC every 8 weeks and 2600 mg/m^2 5-FU and 100 mg/m^2 LV admixed in an outpatient infusion pump administered for 24 hours every week for 6 weeks, followed by a 2-week break. Response and overall survival rates were parallel in these two studies. In addition, 2 patients in our series who had abdominal wall and supraclavicular lymph nodes metastases, respectively, achieved complete remission and had long-term survival (36 and 34 months, respectively). In Kretzschmar's study, grade III/VI toxicity including leukopenia (23%), thrombocytopenia (13%), anemia (10%), and diarrhea (10%), was higher than that in the present series. Although no definite reasons could explain this, we can suggest at least 2 possibilities. The first contributing factor may be due to the higher dose of folinic acid (500 vs. 100 mg/m^2) in combination with 5-FU in the regimen of Kretzschmar et al.[26] The second factor, that we consider to be of even greater importance, is the MMC dose-related myelotoxicity. In contrast to Kretzschmar et al.'s regimen, we admixed FU and LV in the same bag for simultaneous infusion. Ardalan et al.[14] described that a combination of high-dose 5-FU and LV may result in the development of 'calcium-LV stones' which might block the central venous catheter. Subsequently, many studies avoided this by infusing 500 mg/m^2 LV 1-2 hours prior to infusing 5-FU. We found no 'calcium-LV stones' in our patients using the simultaneous infusion of 5-FU and LV.

Adding another active agent, such as CDDP, paclitaxel, epidoxorubicin, or etoposide, to the 24-hour infusion of 5-FU and LV produced similar response rates and acceptable toxicity according to several studies. In 1996, Wilke et al.[27] reported using an identical regimen plus CDDP that produced an overall response rate of 66% and a median survival time of 13 months. The toxicity was higher than that with 5-FU/LV alone, and we also had the

same experience.[18] Bokemeyer et al.[28] used paclitaxel in combination with weekly 24-hour infusions of 5-FU/LV and achieved a response rate of 32% and a median survival of 11 months among 22 patients. Subsequently, they published a study in which they added cisplatin to paclitaxel with weekly 24-hour 5-FU/LV infusions that produced a 51% response rate, with a median survival of 14 months and an acceptable toxicity profile.[29] Chi et al.[30] used weekly 24-hour infusions of high-dose 5-FU/LV with cisplatin, epidoxorubicin, and etoposide and reported only 1% grade IV neutropenia; their response rate was 71% of 42 patients which is the highest among those reported in the literature, but the median survival was only 10 months. Reviewing these reports and our experience, weekly infusions of high-dose 5-FU-based combination regimens have good activity and minimal toxicity for patients with advanced gastric cancer. However, we still need to undertake additional phase III studies to clarify whether adding active agents into weekly infusions of high-dose 5-FU and LV can achieve higher response and survival rates.

MMC with weekly 24-hour infusions of high-dose 5-FU and LV in our dose schedule is a simple, less-expensive treatment and produces activity against advanced gastric cancer with acceptable toxicity. Nevertheless, further randomized studies to confirm the role of MMC with weekly 24-hour infusions of high-dose 5-FU and LV are warranted.

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MMC合併每週24小時高劑量5-FU及LV注射於晚期胃癌病人

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背 景： 我們已經報告過使用每週24小時高劑量5-FU 及LV注射於晚期胃癌病人的經驗，可以達成33%反應率及中位存活7 個月。探討MMC 加入每週24小時高劑 量5-FU 及LV注射是否可以增加反應率及中位存活時間。

方 法： 從1998年5月至2000年12月期間，共有37位廣泛性胃癌未曾化學治療病人接受本治療。其中有20位男性和17位女性，中位年齡爲58歲〔範圍：21至73歲〕。本治療方法爲：每週使用5-FU 2600 mg/m^2 和 LV 100 mg/m^2 混合於門診攜帶型幫浦24小時注射連續6 週再休息2 週，MMC 10mg/m^2 於第一週注射，每8週一次。此治療持續 直到疾病惡化、無法接受之毒性或病人拒絕治療爲止。

結 果： 總共進行404 次5-FU/LV治療，平均10次治療。反應率爲 40.5%〔15/37〕，其中有5.4%〔2/37〕達到完全緩解。時間至疾病惡化爲 4.5月，中位存活期爲8 個月。所有病人都接受毒性評估，少於10%病人有第三級或第四級毒性。

結 論： MMC 合併每週24 小時高劑量5-FU 及LV 注射於晚期胃癌病人具有中度控制能力而且有可以接受之毒性。

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關鍵字： 胃癌，mitomycin C，5-fluorouracil，leucovorin。

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