Phase II Trial of Epirubicin, Cisplatin, Oral Uracil and Tegafur, and Leucovorin in Patients with Advanced Gastric Carcinoma

Yoon T. Jeen, M.D.[1]
So Y. Yoon, M.D.[2]
Sang W. Shin, M.D.[2]
Byung S. Kim, M.D.[2]
Young J. Mok, M.D.[3]
Chong S. Kim, M.D.[3]
Jin H. Hyun, M.D.[1]
Jun S. Kim, M.D.[2]
Yeul H. Kim, M.D.[2]

[1] Department of Gastrointestinal Disease, Korea University, College of Medicine, Seoul, Korea.

[2] Department of Hematooncology, Korea University, College of Medicine, Seoul, Korea.

[3] Department of General Surgery, Korea University, College of Medicine, Seoul, Korea.

Address for reprints: Yeul H. Kim, M.D., Department of Hematooncology, Anam Hospital, Korea University, College of Medicine, 126-1, Anam-Dong 5 Ga, Seongbuk-Ku, Seoul 136-075, Korea; Fax: 82-2-922-5974; E-mail: yhk0215@nownuri.net

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BACKGROUND. The results of chemotherapy for patients with gastric carcinoma generally have been modest, although regimens developed more recently have produced higher response rates. One such regimen is epirubicin, cisplatin, and protracted infusion of 5-fluorouracil (ECF). The advantage of a long-term oral administration of uracil and tegafur (UFT) is that this treatment may be used to mimic the protracted infusion of 5-fluorouracil (5-FU). In addition, UFT treatment combined with leucovorin had a favorable activity and tolerable toxicity in patients with advanced gastric carcinoma. Instead of the inconvenience of an infusion pump and intravenous catheter for the protracted infusion of 5-FU, the authors administered UFT plus leucovorin in an ECF regimen for the treatment of patients with advanced gastric carcinoma.

METHODS. Fifty-two patients with advanced gastric carcinoma received epirubicin, cisplatin, and oral UFT plus leucovorin. Epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 were administered on Day 1 by intravenous injection. Tegafur and uracil 360 mg/m^2/day orally was administered in conjunction with leucovorin administered at a fixed dose of 45 mg/day orally in divided daily doses for 21 days followed by a 7-day rest period. These courses were repeated every 4 weeks. The median age of the patients was 59 years with a median World Health Organization performance status of 1. Patients received a median of five courses of treatment (range, 1–10).

RESULTS. Among the 47 patients evaluated, three patients achieved complete response, and 24 patients had partial responses, for an overall response rate of 57.5% (95% confidence interval, 71.5–43.3%). Stable disease was reported in 11 patients (23.4%), and another 9 patients (19.1%) showed disease progression. The median duration of survival was 15 months (range, 2–33+). The main toxicity was nausea/vomiting and neutropenia. Significant toxicity (modified National Cancer Institute common toxicity Grade 3 or 4) included neutropenia in 22 patients (42%), nausea in 14(27%), vomiting in 9 (18%), oral mucositis in 3 (6%), and diarrhea in 3 (6%) patients.

CONCLUSIONS. The authors conclude that epirubicin, cisplatin, and oral UFT plus leucovorin, a convenient regimen, has a significant activity and tolerable toxicities in patients with gastric carcinoma. ***Cancer* 2001;91:2288–93.**

KEYWORDS: gastric carcinoma, epirubicin, cisplatin, uracil and tegafur (UFT), leucovorin, combination chemotherapy.

Although the incidence of gastric carcinoma has decreased in most Western countries, it remains a significant problem in global health terms as the second most common cause of cancer mortality worldwide.[1] Surgical resection is the only therapeutic modality capable of cure, and improvements in early diagnosis, preoperative as-

sessment, and surgical technique have increased the number of potentially curative resections during the last 20 years. Despite this, the prognosis of the disease remains poor with a 10–15% 5-year survival rate.[2]

The reasons for this grim outlook include the finding that both local and distant recurrence, even after an apparently complete resection, are common and that many patients present with inoperable disease at the time of diagnosis. Given the predominantly palliative intent of advanced gastric carcinoma therapies, regimens with both a low toxicity and an acceptable activity should be chosen for patients in this category.[3]

Several drugs have been shown to have significant activity as a single agent in gastric carcinoma including doxorubicin, mitomycin C, cisplatin, epirubicin, and 5-fluorouracil (5-FU) with response rates of between 19% and 86%.[4] Various combination regimens have been attempted in advanced disease, and there is evidence of improvement in median survival by approximately 7 months when compared with supportive care alone.[5,6]

The combination of epirubicin, cisplatin, and continuous infusion 5-fluorouracin (ECF) was reported in a Phase II study of 139 patients resulting in a 70% response rate in advanced gastric carcinoma.[7] A more recent update of this series from Royal Marsden Hospital reported an overall response rate of 61%. Of those patients with locally advanced disease, 66% had complete surgical resection after ECF with a histologic complete response in 32%.[8] The choice of the three drugs in the regimen was based on their single-agent activity in upper gastrointestinal carcinoma[9–12] and the potential synergy between 5-FU and cisplatin shown in experimental models.[13] An anthracycline was included because of the anticipated enhanced cytotoxicity afforded by combining it with the other two drugs. Evidence for this potential increase in efficacy is provided by the results of a recently reported randomized trial of advanced gastric carcinoma in which the addition of epirubicin to a combination of bolus 5-FU and cisplatin resulted in a significant survival benefit compared with 5-FU and cisplatin alone.[14]

The regimen also was designed to minimize systemic toxicity. Hence, epirubicin was chosen instead of doxorubicin because of its association with lower rates of mucositis and cardiac toxicity.[15] 5-Fluorouracil was administered by protracted venous infusion, because this schedule has been shown to produce higher response rates and less myelotoxicity compared with bolus administration for patients with colorectal carcinoma.[16]

Tegafur is a prodrug of 5-FU that undergoes metabolic activation primarily in the liver. Fujii et al. reported that oral administration of combination tegafur and uracil (UFT) significantly increased 5-FU levels in tumor when compared with tegafur alone.[17] The mechanism for this biochemical modulation is thought to be the inhibitory effect of uracil on the degradation of 5-FU through competition with 5-FU for dihydropyrimidine dehydrogenase.[18] An advantage of the long-term oral administration of UFT is that it might mimic the effects of protracted infusion of 5-FU.

A potential drawback of the ECF regimen is the central venous line, portable infusion pump, and protracted infusion. Therefore, we conducted a Phase II trial of epirubicin, cisplatin, UFT, and leucovorin in which 5-FU is replaced with oral UFT and leucovorin.

MATERIALS AND METHODS

Patients

Between April 1997 and June 1999, 52 patients examined at the Korea University Anam and Guro Hospitals were entered onto the study. Patients with histologically proven metastatic or locally advanced inoperable gastric carcinoma were eligible for this study. Patients were required be a World Health Organization (WHO) performance status of less than or equal to 2. There were no age restrictions. Patients were considered ineligible if they had received previous chemotherapy or radiotherapy, with the exception of postoperative adjuvant chemotherapy, in the previous 6 months. Bidimensionally measurable disease was considered mandatory, even for patients with locally advanced disease, who were required to have at least one enlarged lymph node of greater than 2.5 cm in greatest dimension, assessable by computed tomographic scan, to be considered eligible. All patients were required to have had a leukocyte count greater than or equal to 4000/μL, platelet count greater than or equal to 100,000/μL , creatinine concentration less than or equal to 1.5 mg/dL, and/or creatinine clearance greater than 60 mL/minute, and total serum bilirubin less than 2 mg/dL. The extent of measurable disease was assessed by computed tomographic scan, chest X-ray, and endoscopies. Such examinations were made before the first cycle and after each of the other cycles for a response evaluation. Finally, all patients provided informed consent.

Drug Administration and Dose Adjustments

The treatment schedule was as follows: epirubicin 50 mg/m^2 was given as a bolus intravenous injection every 4 weeks. Cisplatin 60 mg/m^2 also was administered as a 4-hour intravenous infusion every 4 weeks with standard hydration. Cisplatin was administered at full dose for creatinine clearance greater than or

equal to 60 mL/minute; if the creatinine clearance was 40–60 mL/minute, the milligram dose of cisplatin was equal to the creatinine clearance value in milliliters per minutes. For creatinine clearance values less than 40 mL/minute, no cisplatin was administered. For leukocyte counts less than 2.0×10^9/L or platelets less than 100×10^9/L during epirubicin and cisplatin administration, the treatment was delayed for 1 week or until myelosuppression had resolved. A second episode of treatment delay due to myelosuppression or an episode of modified National Cancer Institute (NCI) common toxicity scale Grade 4 myelosuppression required a 25% dose reduction of epirubicin and cisplatin on subsequent treatments. If there were repeated episodes of Grade 3 or 4 myelosuppression, despite dose modification, treatment was withdrawn. Oral UFT and leucovorin were administered for 21 consecutive days of treatment followed by a 7-day treatment free interval. The total daily dose of UFT was divided into three doses administered orally every 8 hours, beginning with an initial dosage of 360 mg/m^2/day. UFT was supplied in the form of 100-mg capsules (i.e., 100 mg tegafur plus 225 mg uracil). Leucovorin was supplied as 5-mg tablets and administered orally, with the total amount divided into three doses. The total daily leucovorin dose was fixed as 45mg (9 tablets). In subsequent courses, the daily dose of UFT was increased by 100 mg/day if toxicity was absent or mild at the starting dose level. The leucovorin dose, however, remained at 45 mg/day on the next course. The daily dose of UFT was reduced by 100 mg/day in patients with Grade 3 or 4 nonhematologic toxicity, based on modified NCI toxicity scale. Oral administration of UFT and leucovorin was interrupted if the patient developed Grade 3 or 4 nonhematologic toxicity that did not resolve with UFT dose reduction. Treatment was reinstituted after the clinical symptoms resolved. Courses were repeated every 4 weeks until tumor progression or the development of treatment intolerance. Complete blood, differential, and platelet counts were evaluated once a week or more frequently when patients were myelosuppressed during the resting period. Serum creatinine, blood urea nitrogen, electrolyte level, and magnesium levels were checked before each chemotherapy cycle.

Assessment of Response and Dose Adjustment

Before entering the study, all patients received a physical examination, full blood count analysis, and serum chemistry analysis. Chest X-ray, electrocardiogram, upper gastrointestinal endoscopies, doubling contrast upper gastrointestinal radiographs, abdominal computer tomographic scans, and other appropriate procedures also were performed. Patients were evaluated weekly using routine blood tests at the outpatient clinic unless the disease progressed unequivocally or the patient had dropped out of the study due to drug toxicity, the disease status was reevaluated radiologically every two cycles. Standard World Health Organization response criteria were used to assess the response to treatment. Toxicity also was reported using modified NCI toxicity scale. The response duration was calculated from the date that the response was confirmed to the date that progressive disease was first observed. The survival duration was calculated from the first day of treatment to death or the last follow-up.

TABLE 1
Patient Characteristics (n = 47)

Characteristic	n
Median age (yrs)	59
Range	(24–77)
Male/female ratio	34/13
WHO performance status	
0	13
1	22
2	12
Prior treatment	
None	43
Adjuvant chemotherapy	4
Site of measurable disease	
Liver	22
Lymph node	17
Others	8

WHO: World Health Organization.

Statistical Analysis

This was a confirmatory, Phase II study whose primary objective was to determine the response rate and toxicity of oral UFT, leucovorin, epirubicin, and cisplatin combination chemotherapy. The secondary objective was to evaluate the survival and duration of response. The 95% confidence interval (CI) for response was calculated. Survival probabilities were estimated using the Kaplan–Meier method

RESULTS

Patient Characteristics

Fifty-two patients were entered into this trial. Patient characteristics are listed in Table 1. Five patients were removed from the study after one or two cycles of treatment due to the refusal of treatment by the patients. These patients are enrolled in the assessment of toxicity but are excluded from the analysis of survival or response. Thirty-five patients (74.5%) had a relatively good performance status of Grade 0 or 1. The

TABLE 2
Treatment Characteristics

Characteristic	*n*
Total no. of treatments	242
Median	5
Range	(1–10)
Dosage level	
0	142
−1 level of epirubicin and cisplatin	49
−1 level of UFT	51
Dose reduction, no. of patients	
−1 level of epirubicin and cisplatin	18
−1 level of UFT	18

UFT: tegafur and uracil.

median age of the patients was 59 years with a range of 24 to 77. Four patients had been treated previously with adjuvant chemotherapy after curative surgery. These patients experienced recurrence with distant metastasis or local recurrence. Treatment off period was 84, 63, 47, and 9 months, respectively. The postoperative chemotherapy regimens were 5-FU plus cisplatin (FP), BCNU plus cisplatin plus 5-FU, mitomycin C plus 5-FU plus ara-C (MFC), 5-FU plus doxorubicin plus mitomycin C (FAM), respectively. Two of these patients achieved a partial response with a response duration of 18+ months and 15+ months. One patient had a stable disease, and the other patient experienced progression.

Response to Chemotherapy

Two hundred forty-two courses of treatment were administered to 52 patients. The median number of courses per patient was 5 with a range of 1 to 10 (Table 2). Overall, at least 95% or more of all drugs were administered per cycle (epirubicin and cisplatin, 94.9%; UFT, 95.8%), with 20 patients (42.5%) requiring dose modification during treatment. With 27 of 47 patients evaluated responding, the overall objective response rate was 57.5% (95% CI, 71.5–43.3%) including 3 (6%) complete responses (Table 3). One patient who had recurring lung metastasis after curative surgical resection achieved a complete response with response duration of 30+ months. Two patients who had liver and regional lymph node metastasis achieved a complete response with a response duration of 15.5+ months and 12+ months. The median survival duration for all patients was 15 months (range, 2–33+ months; Fig. 1).

Toxicity

The main toxicities encountered with epirubicin, cisplatin, oral UFT and leucovorin were neutropenia and vomiting (Table 4). Modified NCI Grade 3 and 4 neutropenia was observed in 7 (13%) and 15 (29%) patients, respectively. Treatment was discontinued in one patient due to prolonged myelosuppression after treatment with a reduced dosage of epirubicin and cisplatin. Grade 3 and 4 vomiting were observed in 7 (13%) patients and 2 (4%) patients, respectively. Three patients experienced Grade 3 diarrhea severe enough

TABLE 3
Treatment Response

Response characteristic	*n*
Total no. of patients assessable for response	47
Complete remission (%)	3 (6.4)
Partial remission (%)	24 (51.1)
Stable disease (%)	11 (23.4)
Progressive disease (%)	9 (19.1)
Median duration of survival in months (range)	15 (2–33+)
Median duration of response in months (range)	12 (2–30+)

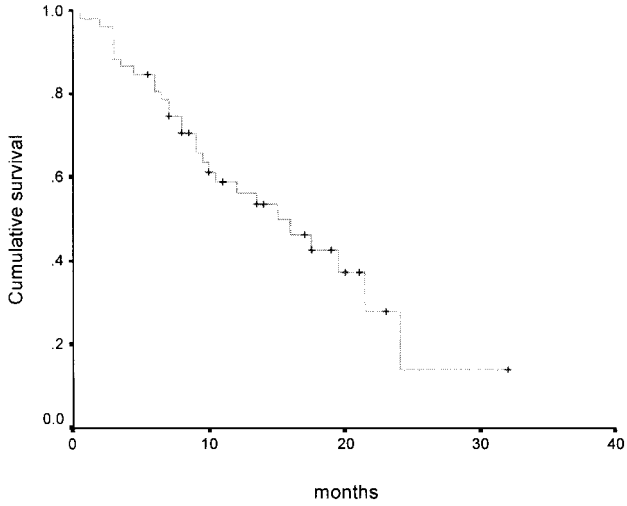

FIGURE 1. Kaplan–Meier estimation of actuarial overall survival for the 47 patients is shown. Median survival duration is 15 months.

TABLE 4
Toxicity: Modified National Cancer Institute Grade (*n* = 52)

	Modified NCI grade (%)			
Toxicity	**1**	**2**	**3**	**4**
Neutropenia	20 (39)	10 (19)	7 (13)	15 (29)
Thrombocytopenia	43 (82)	2 (4)	3 (6)	4 (8)
Nausea	23 (44)	15 (29)	14 (27)	—
Vomiting	27 (52)	16 (31)	7 (13)	2 (4)
Diarrhea	43 (82)	6 (12)	3 (6)	0
Stomatitis/mucositis	41 (79)	8 (15)	3 (6)	0

NCI: National Cancer Institute.

to require temporary cessation of treatments. Grade 3 mucositis occurred in three patients. Neutropenic fever, leading to hospitalization, developed in 6 patients (12%). There was no severe infection or treatment related death.

DISCUSSION

The objective of this study was to assess the efficacy and toxicity of the epirubicin, cisplatin, oral UFT, and leucovorin combination treatment. The result of this study confirms that epirubicin, cisplatin, oral UFT, and leucovorin combination treatment is an active regimen due to its favorable patterns of toxicity and its feasibility on an outpatient basis for the treatment of advanced gastric carcinoma. The clinical objective response rate was 57.5%. Our response rate was inferior to the response rate of ECF that originally was reported by Findlay et al.[7] However, the response rate was similar with that of the Italian Group for the Study of Digestive Tract Cancer (56%) and that reported by Bamias et al.[8], and the 95% CI for the overall response rate of those studies partially overlapped with ours, and the results are comparable to those of the most active regimens reported to date (FAMTX, EAP).[19–22] The efficacy in locally advanced disease is significantly higher than in metastatic disease with objective responses observed in 70% of the patients. These results indicate a possible role in the neoadjuvant setting for downstaging an inoperable tumor. In addition, this possibility is supported by five patients, who underwent surgery after response to chemotherapy. Curative resection was performed in three of five patients who attempted surgery. One patient is in a disease free state with a survival duration of 24+ months. Liver and brain metastasis were developed in the other two patients with a survival duration of 8+ and 21.5 months, respectively. Two patients, who had residual disease after surgery, had survival durations of 19.5 and 16 months.

The main toxicity of this regimen was nausea/vomiting. The incidence of Grade 3 or higher nausea/vomiting was 31%. This regimen has more severe nausea or vomiting episodes than our previous study using oral UFT plus leucovorin.[23] This phenomenon can be explained by the addition of cisplatin and epirubicin. Eighteen patients required dose reduction of UFT during the treatment. Another significant toxicity was myelosuppression. Fifteen patients experienced Grade 4 neutropenia.

There are several possible explanations for the enhanced activity of the epirubicin, cisplatin, UFT, and leucovorin regimen. A pivotal role in the activity of this regimen is likely to be due to the oral administration of UFT. In advanced colorectal carcinoma, preliminary and final results have been published from five randomized trials, which include a protracted infusional 5-FU regimen versus a standard bolus arm.[16] The cumulative overall response rate was 26% (95% CI, 22–30%) for the infusional regimen and 10% for the bolus arm, although no survival differences have emerged. A protracted infusion of 5-FU has resulted in a 31% response rate in a small study of advanced gastric carcinoma.[24] This is likely to be due to the relatively high-dose intensity and the ability to maintain a constant plasma level of 5-FU, which is a cell cycle specific drug with a short half-life of approximately 15 minutes.[25,26] Oral UFT generates plasma 5-FU levels similar to protracted venous infusion of 5-FU.[18] In addition, a potential drawback of protracted venous infusion of 5-FU is the central venous line and the portable infusion pump, which may add morbidity and cost. In our regimen, the protracted venous infusion of 5-FU was replaced by oral UFT plus leucovorin, which has a proven clinical activity in advanced gastric carcinoma patients. Another explanation for the activity of this regimen also may be represented by the well known synergism between cisplatin and 5-FU. The cell killing performed by these two drugs may recruit a proportion of tumor cells into the cell cycle that becomes more sensitive to the antineoplastic activity of prolonged 5-FU infusion. Preclinical studies have suggested that 5-FU and cisplatin may be synergistic due to cisplatin-induced depletion of intercellular methionine, which results in the enhanced binding of fluorodeoxyuridine monophosphate to thymidylate synthase.[27] Anthracyclines have been known to be active in gastric carcinoma, and epirubicin was incorporated into the regimen because it is less likely to cause mucositis than doxorubicin, and thereby less likely to enhance 5-FU–related mucositis.[28] The median survival duration for all patients was 15 months. This result appears to be much better than the survival observed in untreated patients with metastatic or unresectable gastric carcinomas, among whom the reported median survival times range from 2 to 4 months.[29] Furthermore, side effects of this regimen were tolerable and controllable. Because of the 1-day infusion schedule, this regimen can be administered on an outpatient basis without disrupting daily life. With the oral treatment regimen, treatment may be temporally discontinued if symptoms of toxicity such as diarrhea, mucositis, nausea, or vomiting worsen. In conclusion, oral UFT, leucovorin, epirubicin, and cisplatin combination chemotherapy is an innovative regimen of proven activity in advanced gastric carcinoma and is characterized by a favorable toxicity pattern. This regimen may provide an option as adjuvant chemotherapy, because of its convenience

to administer, high activity, and manageable toxicity. In addition, the ability of this regimen to downstage tumors may enable the resection of unresectable gastric carcinoma with a preoperative approach.

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