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Epirubicin, Cisplatin, and Protracted Venous Infusion of 5-Fluorouracil for Advanced Gastric Carcinoma

To evaluate the activity and safety of a combination chemotherapy with epirubicin, cisplatin, and a protracted venous infusion of 5-fluorouracil (ECF) in unresectable or metastatic gastric cancer, a phase II study was performed. Thirty-five chemotherapy-naive patients were given ECF. Epirubicin (50 mg/m^2 intravenous, IV) and cisplatin (60 mg/m^2 IV) were administered every three weeks during a continuous intravenous infusion of 5-fluorouracil (250 mg/m^2/day) using infusion pump. One complete response and 19 partial responses (response rate=62%) were achieved. Eight patients remained stable, whereas in four patients the disease progressed. The median duration of response was 22 weeks (95% confidence interval, 18-27 weeks). The median survival for all patients was 10 months (95% confidence interval, 6-14 months), with a 1-yr survival rate of 40%. A total of 184 cycles of chemotherapy were administered. Grade 3 or 4 emesis occurred in 3%, mucositis in 2%, anemia in 10%, and leukopenia in 3% of the cycles. Central venous catheter complications that required line removal occurred in 37% (n=13) of the patients. No patient died of toxicity. Overall, the ECF regimen showed high anti-tumor activity with a tolerable toxicity pattern.

Key Words : *Gastrointestinal Neoplasms; Epirubicin; Cisplatin; Fluorouracil; Infusion Pumps*

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INTRODUCTION

Despite improvements in early diagnosis, many patients diagnosed with gastric cancer are inoperable at the time of initial diagnosis. Even after intended curative resection, local, regional, and distant recurrences develop in more than 80% of patients. Advanced gastric carcinoma remains an incurable disease with a median survival of 6 to 9 months. Two randomized trials have shown that a combination chemotherapy may provide a significant survival benefit and offer an improved quality of life to patients with the advanced gastric carcinoma when compared with best supportive care (1, 2).

In the 1980s, the FAM (5-fluorouracil, doxorubicin, and mitomycin-C) regimen was prematurely adopted as the standard therapy for advanced gastric cancer. However, a prospective randomized study later showed that the FAM regimen had no survival benefit and more severe toxicity than single-agent 5-fluorouracil (5-FU) treatment (3). One of the few studies to show a small but significant survival benefit compared FAMTX (5-FU, doxorubicin, and methotrexate) with FAM, and the FAMTX was found to have higher response rates (41% versus 9%) and longer duration of survival (42 vs 29 weeks) than FAM (4).

5-FU given as a continuous intravenous infusion at a dose of 300 mg/m^2/day has been shown to elicit higher response rates and less myelotoxicity than intermittent bolus administration in patients with colorectal cancer (5). The cumulative overall response rate was 26% (95% confidence interval, CI, 22% to 30%) for the infusional regimen and 10% (95% CI, 6% to 14%) for the bolus arm, although no survival differences were apparent. In addition to advanced colorectal cancer, a protracted infusion of 5-FU resulted in a high response rate (31%) in a small study of advanced gastric cancer (6). A regimen of epirubicin, cisplatin, and a protracted infusion of 5-FU (ECF) was prescribed, based on the single-agent activity of each agent in upper gastrointestinal cancer and on the synergy between 5-FU and cisplatin already demonstrated in experimental models (7). In a randomized trial, 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 only in advanced gastric cancer (8). In phase II studies with ECF, including the protracted infusion of 5-FU, response rates of over 50% were reported, with apparently moderate toxicity and satisfactory symptom control (9-11). Moreover, the ECF regimen, including the protracted infusion of 5-FU, resulted in a higher response rate (45% vs 21%) and longer survival duration (8.9 months vs 5.7 months) than FAMTX, with less myelosuppression, less mucositis, and better quality of life in randomized trials by Webb et al. and Waters et al. (12, 13). Therefore, we con-

ducted a phase II study to confirm the activity and feasibility of an ECF regimen, including a protracted infusion of 5-FU, in patients with metastatic gastric cancer.

MATERIALS AND METHODS

Eligibility criteria

Patients enrolled in this study were required to fulfill the following eligibility criteria: (1) histologically proven adenocarcinoma of the stomach with measurable metastatic lesions; (2) an unresectable tumor, locally advanced, metastatic, or relapsed after resection; (3) aged 70 yr or younger; (4) no previous chemotherapy or radiation therapy, though prior adjuvant chemotherapy was allowed (>6 months apart); (5) Eastern Cooperative Oncology Group scale performance status of 2 or less; (6) adequate bone marrow (WBC $\geq$4,000/μL, platelet $\geq$100,000/μL), liver (serum bilirubin level $\leq$2.0 mg/dL and serum transaminase level $\leq$100 IU/dL), and renal (serum creatinine level $\leq$1.5 mg/dL) functions; (7) normal cardiac function; (8) no other severe medical condition; (9) a life expectancy of at least 3 months; and (10) must have given written informed consent before being enrolled in the study.

Treatment schedule

Chemotherapy was administered through a central venous catheter placed in the subclavian vein. 5-FU was given as continuous intravenous (IV) infusion at a dose of 250 mg/m^2/day using a portable pump (I-Flow Corporation, California, U.S.A.). Epirubicin (50 mg/m^2 IV) and cisplatin (60 mg/m^2 IV infusion with adequate hydration) were given on Day 1 every 3 weeks to a maximum of nine cycles. Central venous catheters were changed every 3 cycles to prevent catheter-related complications. Granisetron was used routinely before administration of cisplatin as a prophylactic antiemetics.

Toxicity assessment and dose modifications

Toxicity was graded according to the National Cancer Institute (NCI) common toxicity criteria version 2.0. For patients with Grade 3 or 4 non-hematologic toxicity, ECF administration was interrupted until symptoms had resolved and then restarted with a 25% dose reduction for Grade 3 toxicity and a 50% dose reduction for Grade 4. Patients developing hand-foot skin reactions were given 50 mg of pyridoxine three times daily. If symptoms failed to improve, 5-FU was discontinued for 1 week and restarted with a 25% dose reduction for Grade 3 toxicity. Cisplatin was administered at full dose when the glomerular filtration rate (GFR) was equal to or greater than 60 mL/min; if the GFR was 40-60 mL/min, the dose of cisplatin in milligram equaled the GFR value in milliliters per minute. No cisplatin was administered when the GFR value was less than 40 mL/min.

If the leukocytes count was less than 3,000/μL or platelets were less than 100,000/μL on the first day of treatment, ECF administration was delayed for 1 week or until myelosuppression resolved. A second episode of treatment delay due to myelosuppression or an episode of neutropenic sepsis required a 25% dose reduction of 5-FU and epirubicin on subsequent treatments. If there were repeated episodes of Grade 3 or 4 toxicity in spite of dose modification, the treatment was stopped.

Superficial infection of the indwelling catheter was treated with antibiotics according to bacteriological results. Indwelling catheters were removed in the following situations: septicemia due to catheter infection, catheter infection worsening despite appropriate antibiotic treatment, catheter thrombosis, intolerable shoulder pain.

Assessment of response and statistical analysis

Before entering the study, all patients received a physical examination, a complete blood count analysis, serum chemistry analysis, a chest radiography, an electrocardiogram, and an abdominal computed tomographic scan with endoscopy. The primary objectives of this study were to determine the response rate and the toxicity of the ECF regimen. The secondary objectives were to evaluate the survival rate and the duration of response of the regimen.

Objective response to chemotherapy in measurable lesions was evaluated using the standard World Health Organization criteria. In addition to the WHO criteria, histologic confirmation of endoscopic findings was required to classify a response at the primary site as complete, and only measurable lesions were considered assessable for response evaluation. Time to progression was measured in all patients from the beginning of chemotherapy to the first evidence of progression; duration of response was calculated in responding patients from the first evidence of response to the date of progression or death; duration of survival was calculated from the beginning of treatment until the date of death. Curves were plotted using the Kaplan-Meier method and compared using the log rank test.

RESULTS

Characteristics of the patients

Thirty-five patients were enrolled in the study from May 1999 to March 2001. Thirty-two were assessable for response and thirty-five for toxicity. Two patients were lost to follow-up after the second cycle and before the first evaluation of response. One patient experienced Grade 3 mucositis after the first cycle and refused further therapy. Characteristics of the

patients are listed in Table 1. The median age of the advanced gastric cancer patients was 56 yr (range 36-68). Metastatic sites were lymph node (n=28), peritoneum (n=9), liver (n=8), adrenal gland (n=2), lung (n=1), and others (n=5). Patients with peritoneal metastasis had other measurable metastatic lesions. Thirty-four patients had had no previous chemotherapy. One patient had received adjuvant chemotherapy with 5-FU and mitomycin for 6 months, 2 yr prior to the ECF chemotherapy.

Tumor response

Objective responses were seen in 20 of 32 (62%) patients, with one patient (3%) achieving a complete response and 19 (59%) showing partial responses. Eight patients remained stable, whereas four progressed. Median response duration (Fig. 1) and time to progression were 22 weeks (95% CI, 18 to 27 weeks) and 25 weeks (95% CI, 18 to 32 weeks), respectively. Median survival for all patients was 10 months (95% CI, 6 to 14 months), with a 1-yr survival rate of 40% (Fig. 2).

Toxicity

A total of 184 cycles were delivered, with a median of 6 cycles per patient (range, 1-9 cycles). Overall, 92% of the planned epirubicin dose was administered per course, 93% of the planned 5-FU dose, and 94% of the planned cisplatin dose, although dose reductions were required in 23 patients (65%).

Toxicity is shown in Table 2. Grade 3 or 4 emesis occurred in 3%, mucositis in 2%, anemia in 10%, and leukopenia in 3% of the cycles. Treatment was delayed due to myelosuppression in 13 (7%) of the 184 cycles. Central venous catheter complications requiring line removal occurred in 37% (n=13) of the patients. Other catheter-related complications were shoulder pain (n=10), infection (n=7), thrombosis (n=2), line slippage (n=2), and pneumothorax (n=2). No complication was life-threatening or resulted in a long-term morbidity.

Table 1. Patient characteristics

Characteristics		No. (%)
Age (yr)	Median (range)	56 (36-68)
Sex	Male	28 (80)
	Female	7 (20)
Performance status	ECOG 0-1	28 (80)
	2	7 (20)
Extent of disease	Locally advancecd	8 (23)
	Metastatic	25 (71)
	Relapse	2 (6)
Metastatic site	Lymph Node	28
	Peritonium	9
	Liver	8
	Adrenal gland	2
	Lung	1
	Others	5
Prior chemotherapy	No	34
	Yes	1

Table 2. Toxic reactions

Grade (%)	1	2	3	4
Hematologic				
Leukopenia	58 (32)	36 (20)	4 (2)	2 (1)
Anemia	62 (34)	44 (24)	16 (9)	2 (1)
Thrombocytopenia	12 (7)	4 (2)	1 (0.5)	-
Nonhematologic				
Nausea	76 (41)	78 (42)	6 (3)	-
Vomiting	29 (16)	24 (13)	4 (2)	1 (0.5)
Mucositis	17 (9)	13 (7)	4 (2)	-
Diarrhea	8 (4)	2 (1)	1 (0.5)	-
Neuropathy*	12 (34)	7 (20)	-	-
Hair loss*	24 (69)	9 (26)	-	-
Hand-foot skin reaction*	6 (17)	3 (9)	-	-
Total	184 cycles			

*Maximum toxicity experienced by each patient (%).

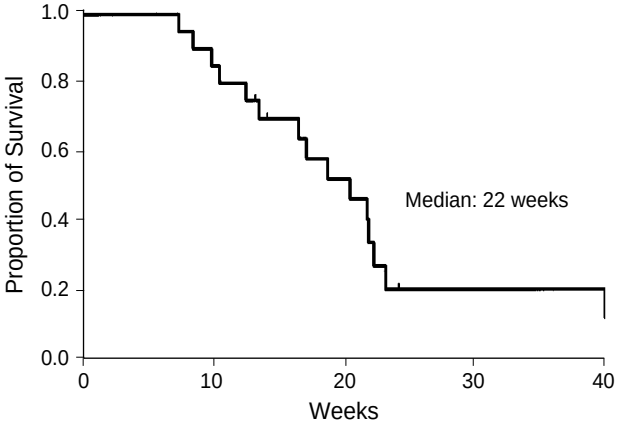

Fig. 1. Duration of response of responsive patients in advanced gastric cancer.

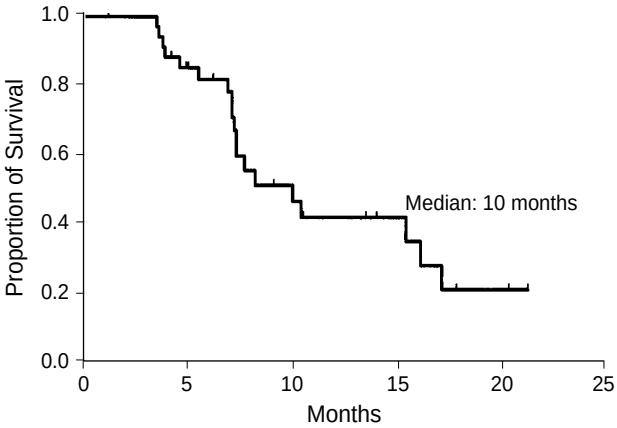

Fig. 2. Overall survival of all patients in advanced gastric cancer.

DISCUSSION

Patients with unresectable gastric cancers have an extremely poor prognosis, with 5-yr survival rates ranging from 5% to 15%. Numerous attempts have been made to develop more effective combination chemotherapy regimens using known active drugs. The FAM regimen became the preferred treatment in the 1980s. A FAM variant, which incorporates a high-dose methotrexate instead of mitomycin (FAMTX), was heralded as having impressive activity. In a direct comparison with FAM, FAMTX proved to be significantly superior in terms of response rate (41% vs 9%; p=0.0001) and median survival duration (9.7 months vs 6.7 months; p=0.004), and was demonstrated to have acceptable toxicity (4). The activity of cisplatin as a single agent in gastric cancer, and evidence that in combination with etoposide it might may be helpful in overcoming multidrug resistance, led to the development of a new combination regimen with increased response rates but considerable toxicity (14). Specifically, in a randomized comparison with FAMTX, etoposide, doxorubicin, and cisplatin (EAP) was found to be no more active, and significantly more toxic (15).

ECF, including a protracted infusion of 5-FU, showed high response rates and median survival durations with tolerable toxicity in phase II trials (9-11). The response rates of this regimen, in studies by Findlay et al. (9), Zaniboni et al. (10), and Bamias et al. (11), were 71%, 56%, and 61%, median survival durations were 8.2 months, 9+ months, and 8.4 months, and treatment-related mortalities were 4.3%, 0%, and 2.5%, respectively. Because these works reported low toxicities, we used a higher dose of the protracted 5-FU infusion (250 mg/ m^2/day) than had been used in the other studies (200 mg/m^2/day) in the hope of obtaining better responses; however, toxic reactions and responses did not increase. The majority of toxic reactions in our study were Grade 1-2, and no one died of toxicity. The response rate (62%) and median survival duration (10 months) in our study were similar to those of the above-mentioned three studies. However, complete remission rate was lower than reported previously (3% vs 12%, 15%, and 11%). This discrepant result might be due to differences in the inclusion criteria or to the variable criteria used to interpret complete response, i.e., based on CT scans or endoscopy of the primary lesion.

The prolonged intravenous administration of 5-FU offers two main advantages when compared with a bolus schedule: a greater dose intensity and a better pharmacologic match to the indolent cell kinetics characteristic of most human solid tumors. Several randomized trials comparing the protracted infusional 5-FU regimen versus a standard bolus arm have demonstrated that a protracted infusion of 5-FU has resulted in a high response rate in advanced colorectal or gastric cancer. Experimental data strongly suggest that continuous exposure to 5-FU provides a superior antimetabolic effect in terms of thymidylate synthase inhibition in human gastric cancer specimens (16). Anthracyclines are known to be active in gastric cancer, and epirubicin was incorporated into the regimen as it is less likely to cause mucositis and cardiac toxicity than doxorubicin. Cisplatin infused with 5-FU in preclinical studies showed synergistic activity due to the cisplatin-induced deletion of intercellular methionine, which results in enhanced binding of fluorodeoxyuridine monophosphate to thymidylate synthase (17).

Despite higher response rates and lower toxicity, a potential drawback of ECF may be the poor patient acceptability of the indwelling catheter and presence of the external infusion pump. The most frequent central venous catheter complication was shoulder pain, which disappeared two or three days after catheter insertion in some of the patients; however, in a few cases the catheter was removed due to pain. Other complications were catheter infection, catheter slippage, thrombosis, and pneumothorax. Central venous catheter complications requiring line removal developed in 37% (n=13) of patients. Thus, new methods that maintain a constant concentration of 5-FU in the blood without the use of a catheter have been developed. Prodrugs of 5-FU such as UFT or capecitabine can maintain a constant 5-FU level through long-term oral administration. A phase II trial of epirubicin, cisplatin, UFT, and leucovorin including oral uracil and tegafur instead of 5-FU showed a 57.5% response rate and 15 months median survival duration (18). A clinical study on an oral capecitabine-based combination regimen, instead of continuous infusion to achieve a constant 5-FU level in blood, was also reported. Capecitabine and cisplatin combination chemotherapy showed a 51% response rate and a median time to progression of 144 days with acceptable toxicity (19).

The routine use of palliative chemotherapy in patients with advanced gastric cancer remains controversial. The use of chemotherapy in advanced gastric cancer is justified in selected patients, e.g., in younger patients with a good performance status, low tumor burden, and no other serious medical condition, after adequately informing patients of potential gains and risks (20). A new agent that is more active and less toxic is required. In a phase II trial, docetaxel, irinotecan, and paclitaxel as single agents showed response rates of 24%, 18%, and 17-23%, respectively, in previously untreated advanced gastric cancer patients (21-23). It is likely that these agents will be further evaluated as candidate agents for new combination chemotherapy regimens.

In conclusion, the ECF regimen is very active and well tolerated in advanced gastric carcinoma. This regimen could be studied in a postoperative adjuvant setting to improve survival in gastric carcinoma. New methods or drugs should also be developed to solve catheter-related problems.

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