A phase II study of intra-arterial chemotherapy of 5-fluorouracil, cisplatin, and mitomycin C for advanced nonresectable gastric cancer

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The best choice of chemotherapy regimen for patients with advanced gastric cancer (AGC) is still a matter of controversy and requires further investigation. This study was performed to evaluate the efficacy and safety of intra-arterial infusion chemotherapy of 5-fluorouracil 1000 mg/m^2, cisplatin 50 mg/m^2, and mitomycin C 10 mg/m^2 (FCM) repeated every 6 weeks, as first-line treatment for AGC. Forty-seven (95.9%) of the 49 patients were assessable for response. Four cases of complete response and 28 cases of partial response were confirmed, giving an overall response rate of 65.3% [95% confidence interval (CI): 52.0–78.6%]. The median time to progression and overall survival for all patients was 8.3 months (95% CI: 6.8–9.8 months) and 14.5 months (95% CI: 12.0–17.0 months). The estimate of overall survival at 12 and 24 months was 55.1% (95% CI: 41.2–69.0%) and 18.4% (95% CI: 7.5–29.2%), respectively. Most patients experienced neutropenia during their course of therapy with 21.3% of patients (n=10) for grade 3/4 neutropenia. Grade 3 stomatitis, lethargy, and palmar-plantar erythema were observed in two (4.3%), eight (17.0%), and one (2.1%) patients, respectively. Yet, no grade 4 nonhematological toxicity was observed. Intra-arterial infusion chemotherapy of 5-fluorouracil 1000 mg/m^2, cisplatin 50 mg/m^2, and mitomycin C 10 mg/m^2 is a tolerated treatment modality with promising activity in patients with previously untreated AGC. *Anti-Cancer Drugs* 20:941–945 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Although the incidence of gastric carcinoma has fallen in most Western countries, it remains a significant problem in terms of global health and is the second most common cause of cancer mortality worldwide [1]. Gastric cancer is often diagnosed at a very advanced stage, with approximately half of all patients presenting with unresectable, locally advanced, or metastatic disease. Four randomized studies comparing best-supportive care with best-supportive care and chemotherapy for advanced gastric cancer (AGC) have shown that chemotherapy can improve survival and quality of life (QoL) [2–5]. Since then, various combination chemotherapy regimens and methods were tested in trials in patients with AGC. The development of more effective and less toxic treatment options for gastric cancer is the goal of many researchers.

Intravenous (i.v.) chemotherapy is usually performed, but for improved curability or operability, intra-arterial chemotherapy has also been performed effectively [6,7]. Kosaka *et al.* [7] investigated the therapeutic efficacy of intra-arterial infusion chemotherapy for AGC, and found that the response rate (RR) of tumors to intra-arterial infusion chemotherapy was significantly higher than that to systemic infusion chemotherapy (31 vs. 13%). The theoretical advantages of intra-arterial chemotherapy over i.v. chemotherapy are that it provides increased drug concentrations at the tumor site and decreased systemic drug levels and toxicity, and allows for continuous tumor exposure to chemotherapeutic agents with the possibility of systemic rescue. The lymph nodes draining the stomach (which are also supplied by the celiac axis) receive cytotoxic perfusion, and the liver is also infused directly by higher concentrations of cytotoxic agents from both the hepatic artery and the portal venous circulation [8]. On the basis of these encouraging results, we conducted a phase II trial to assess the efficacy and safety of intra-arterial infusion chemotherapy of 5-fluorouracil (5-FU), cisplatin, and mitomycin C (MMC) for previously untreated patients with AGC.

Patients and methods

Eligibility criteria

All the patients involved in this study had histologically confirmed metastatic or recurrent gastric adenocarcinoma

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with at least one unidimensionally measurable lesion (i.e. a diameter ≥ 1 cm, as assessed by spiral computed tomography). The patients were 18–75 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group scale. Furthermore, adequate hematological (absolute neutrophil count $\geq 1.5 \times 10^9$/l, platelet count $\geq 100 \times 10^9$/l, hemoglobin ≥ 9 g/dl), renal (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 50 ml/min), and hepatic (total bilirubin ≤ 2.0 mg/dl and serum transaminase level ≤ 3 times the upper limit of the normal range) levels were also required. Patients who had received adjuvant chemotherapy completed 6 months before entry were eligible. Patients were ineligible if they had previously received palliative chemotherapy or radiation therapy, or had other severe medical illnesses, CNS metastasis, another active malignancy, or history of anaphylaxis to drugs. The institutional review board of the author's institution approved the protocol, and written informed consent was obtained from all patients before enrollment.

Catheterization technique

Under local anesthesia, percutaneous femoral artery puncture was accomplished by the Seldinger technique. The catheter was directed to a superselective location by manipulation through the abdominal aorta and celiac axis and into the left gastric artery, or through the common hepatic and then the gastroduodenal artery into the right gastroepiploic artery. Distal placement in the arterial supply to the involved organ distinguishes superselective intra-arterial chemotherapy from regional infusions delivered through a more proximal vessel. The choice of which vessel to use for this selective catheterization was dependent on the location of the tumor. In patients whose tumors were located on the lesser curvature, the left gastric artery was catheterized; in patients whose tumors were located on the pylorus, greater curvature, or fundus, the right gastroepiploic artery was catheterized. The catheter was positioned in the artery as close to the neoplasm as possible so that the infusion bathed the bulk of the tumor but spared normal tissue to the extent possible. Angiographic checks of catheter position and arterial distribution were performed before each chemotherapy infusion to ensure satisfactory positioning of the catheter. The catheter was removed under fluoroscopic guidance immediately after infusion.

Chemotherapy regimen

5-FU 1000 mg/m^2, cisplatin 50 mg/m^2, and MMC 10 mg/m^2 were selected as the intra-arterial chemotherapy agents. Treatment was repeated every 6 weeks. Treatment was administered biweekly until evidence of progression, unacceptable toxicity, patient refusal or for a maximum of six cycles. To prevent nausea and vomiting, 5-HT$_3$ antagonists i.v. and dexamethasone 16 mg i.v. were administered before chemotherapy, and 5-HT$_3$ antagonists were given orally at standard doses 2 days after chemotherapy. Atropine 0.25 mg was given subcutaneously in case of cholinergic syndrome, and was given prophylactically in the following cycles. Loperamide 2 mg orally every 2 h and oral rehydration were prescribed in case of delayed diarrhea. No prophylactic granulocyte colony-stimulating factors were recommended for neutropenia.

Response to treatment and adverse effects

Before entering the study, all patients underwent a physical examination, and full blood count and serum chemistry analyses. Chest radiograph, ECG, upper gastrointestinal endoscopies, abdominal computer tomographic (CT) scans, and other appropriate procedures were also carried out. Patients were given a physical examination, a subjective/objective symptom evaluation, and routine blood tests twice weekly. Every 4 weeks, a biochemistry blood examination was added to this basal evaluation. After every two cycles of treatment, the response was evaluated using Response Evaluation Criteria In Solid Tumors. Of the lesions observed before treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial or complete response (CR), a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was reported using a National Cancer Institute-Common Toxicity Criteria version 2.0 toxicity scale.

Statistical analysis

The current trial used a two-stage optimal design, as proposed by Simon [9], with an 80% power to accept the hypothesis and a 5% significance to reject the hypothesis. In addition, the current trial was designed to detect a RR of 40% as compared with a minimal, clinically meaningful RR of 20%. Allowing for a follow-up loss rate of 10%, the total sample size was 48 patients with a measurable disease. All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response, time to progression (TTP), and survival analyses were all estimated by using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of a CR or a partial response (PR) until the evidence of disease progression was found. Meanwhile, the TTP was calculated from the initiation of chemotherapy to the date of disease progression, whereas the overall survival (OS) was measured from the initiation of chemotherapy to the date of the last follow-up or death. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, Illinois, USA).

Results

Patient characteristics

From March 2004 to June 2007, a total of 49 patients were enrolled into the study from departments of Interventional Radiology, Shanghai 10th People Hospital, Tongji University. The characteristics of the patients are

summarized in Table 1. The median age was 56 (range, 23–74) years, with 36 male patients and 13 female patients. The majority of the patients (93.9%) had an Eastern Cooperative Oncology Group performance status of either 0 or 1. Forty (81.6%) patients presented with metastatic disease, whereas nine patients presented with locally advanced disease. Twenty-six (53.1%) patients presented with recurrent disease after prior gastrectomy (total or subtotal gastrectomy of the primary tumor), 23 patients were newly diagnosed. Twenty-eight (57.1%) patients were diagnosed with poorly differentiated adenocarcinoma. Distant lymph nodes, peritoneum, or liver were the most common sites of the metastatic disease. No patients had received prior palliative chemotherapy or radiotherapy.

Efficacy and survival

Forty-seven (95.9%) of the 49 patients were assessable for response, of the two patients not assessable, both were lost to follow-up after the first cycle of the treatment. All efficacy data are reported using the intention-to-treat principle. Four cases of CR and 28 cases of PR were confirmed, giving an overall response rate (ORR) of 65.3% [95% confidence interval (CI): 52.0–78.6%] (Table 2). Of 32 responses, 24 were patients with metastatic disease, eight were recurrent disease; 18 (56.3%) were observed after two cycles, 10 (31.3%) after four cycles, and four (12.5%) after six cycles of chemotherapy. Of the four cases of CR, three were with liver metastasis, one was with lymph node metastasis. The median follow-up period was 24.5 months. The median TTP for all patients was 8.3 months (95% CI: 6.8–9.8 months). The estimated median OS was 14.5 months (95% CI: 12.0–17.0 months) (Fig. 1). The estimate of OS at 12 months and 24 months were 55.1% (95% CI: 41.2–69.0%) and 18.4% (95% CI: 7.5–29.2%), respectively. Among the 32 responses, there were 15 patients successfully undergoing radical gastrectomy after four cycles of intra-arterial infusion chemotherapy, and all lived longer than 1 year.

Table 1 **Patient characteristics**

Characteristics	Number of patients $N=49$, *n* (%)
Age (years)	
Median (range)	56 (23–74)
Sex	
Male	36 (73.5)
Female	13 (26.5)
ECOG performance status	
0	7 (14.3)
1	39 (79.6)
2	3 (6.1)
Disease status	
Metastatic	40 (81.6)
Locally advanced	9 (18.4)
Newly diagnosed	23 (46.9)
Recurrent	26 (53.1)
Histology	
Well-differentiated AC	4 (8.2)
Moderately differentiated AC	14 (28.6)
Poorly differentiated AC	28 (57.1)
Signet ring cell carcinoma	3 (6.1)
Metastatic sites	
Lymph node	38 (77.6)
Liver	12 (24.5.6)
Peritoneum	11 (22.4)
Ovary	4 (8.2)
Bone	3 (6.1)
Number of metastases	
0	9 (18.4)
1	17 (34.7)
2	18 (36.7)
≥ 3	5 (10.2)

AC, adenocarcinoma; ECOG, Eastern Cooperative Oncology Group.

Table 2 **Tumor response (intention-to-treat analysis)**

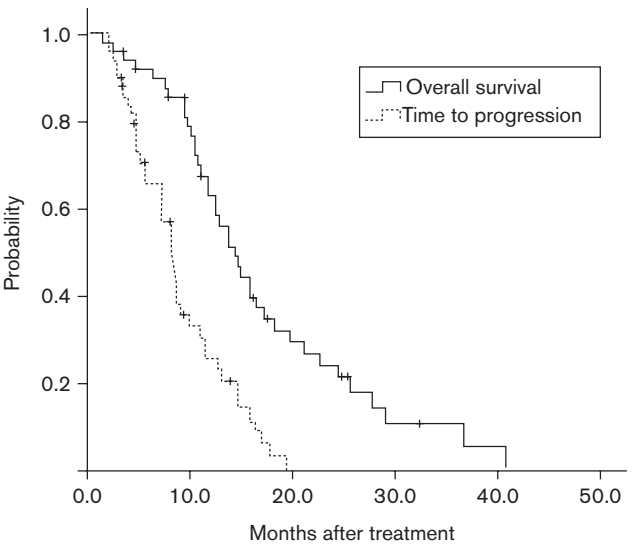
Response	Number of patients $N=49$, *n* (%)
Confirmed response	32 (65.3)[a]
Complete response	4 (8.2)
Partial response	28 (57.1)
Stable disease	7 (14.3)
Progressive disease	10 (20.4)
Not assessable	2 (4.1)

[a]95% confidence interval=52.0–78.6%.

Toxicity

Forty-seven (95.9%) patients were assessable for safety. Toxic effects observed during the study are listed in Table 3. The most common toxic effects were anemia, neutropenia, stomatitis, lethargy, and palmar-plantar erythema. Most patients experienced neutropenia during their course of therapy, with 17.0% of patients ($n=8$) for grade 3 and 4.3% ($n=2$) for grade 4 neutropenia. Grade 1 or 2 neutropenia was detected in 31.9% of patients ($n=15$). Grade 3 anemia and febrile neutropenia were documented in one (2.1%) and two (4.3%) patients, respectively. Stomatitis, lethargy, and palmar-plantar

Fig. 1



Progression-free survival and overall survival for all patients.

Table 3 Toxicities of 5-FU, cisplatin, and mitomycin combination chemotherapy (by patients)

	Grade [number of patients $N=47$, n (%)][a]			
	1	2	3	4
Hematologic				
Anemia	4 (8.5)	3 (6.4)	1 (2.1)	–
Neutropenia	10 (21.3)	5 (10.6)	8 (17.0)	2 (4.3)
Febrile neutropenia	9 (19.1)	6 (12.8)	2 (4.3)	–
Thrombocytopenia	2 (4.3)	1 (2.1)	–	–
Nonhematologic				
Anorexia	6 (12.8)	2 (4.3)	–	–
Nausea/vomiting	9 (19.1)	8 (17.0)	–	–
Stomatitis	4 (8.5)	11 (23.4)	2 (4.3)	–
Alopecia	3 (6.4)	6 (12.8)	–	–
Lethargy	11 (23.4)	6 (12.8)	8 (17.0)	–
Diarrhea	11 (23.4)	12 (25.5)	–	–
Constipation	4 (8.5)	1 (2.1)	–	–
Peripheral neuropathy	8 (17.0)	6 (12.8)	–	–
Palmar-plantar erythema	4 (8.5)	3 (6.4)	1 (2.1)	–

[a]National Cancer Institute common toxicity criteria version 2.0.

erythema were the most common nonhematological toxicities. Grade 3 stomatitis, lethargy, and palmar-plantar erythema were observed in two (4.3%), eight (17.0%), and one (2.1%) patients, respectively. However, no grade 4 nonhematological toxicity was observed in this study. Mild to moderate diarrhea, which was reversible and manageable, developed in 48.9% of the patients. No patients were discontinued from the study because of toxic effects. There were no treatment-related deaths during this study.

Discussion

AGC still has a poor prognosis, with a median survival of just 7–10 months. Several combination regimens of chemotherapy have been developed, but the survival advantage seems to be marginal, and no worldwide standard regimens have as yet been established [10]. The phase III trial, V-325 trial, compared docetaxel, cisplatin, and 5-FU (DCF) with the reference regimen of cisplatin and 5-FU and showed significant superiority of DCF in terms of survival (9.2 vs. 8.6 months), TTP (5.6 vs. 3.7 months), and RR (37% versus 25%) than cisplatin and 5-FU arm [11]. As DCF is an intensive combination with the incidence of grade 3–4 neutropenia of 82%, the benefit-to-risk ratio should be cautiously determined in incorporating the regimen in practice, especially in an elderly population.

This phase II study showed that intra-arterial infusion chemotherapy of 5-FU 1000 mg/m^2, cisplatin 50 mg/m^2, and MMC 10 mg/m^2 repeated every 6 weeks was active and well tolerated as first-line therapy in patients with AGC. The ORR was 65.3%, after a median follow-up of 24.5 months, median TTP was 8.3 months and median OS was 14.5 months. Administration of the same regimen of chemotherapy drugs for superselective intra-arterial chemotherapy in our study showed a significant survival benefit for patients with AGC in comparison with other studies involving traditional i.v. chemotherapy [12–15]. It was reported that serum concentration of chemotherapy drugs in abdominal organs by local intra-arterial infusion was nearly 10 times as high as systemic chemotherapy [16]. One could hypothesize that superselective intra-arterial chemotherapy would only benefit unresectable patients where tumors are isolated to the region of perfusion (i.e. locally AGCs). Patients with liver metastases would also benefit because venous drainage of the chemotherapy perfusion is through the portal circulation [17]. The result of the current study is comparable with the results of similar published reports. Kosaka *et al.* [7] investigated the therapeutic efficacy of intra-arterial infusion chemotherapy for AGC, and found that the RR of tumors to intra-arterial infusion chemotherapy was significantly higher than that to systemic infusion chemotherapy. Liu [18] reported that the ORR to preoperative interventional chemotherapy was 72.8% for gastric carcinomas. However, the influence of intra-arterial infusion chemotherapy on the prognosis of patients with gastric cancer has been controversial. Masuyama *et al.* [19] concluded that intra-arterial infusion chemotherapy might prevent local and lymph node metastases, but it could not improve the survival of gastric cancer patients; whereas Shchepotin *et al.* [17] reported that superselective intra-arterial chemotherapy conferred a highly significant survival advantage compared with control or systemic i.v. chemotherapy for advanced nonresectable gastric cancer.

An important finding from our phase II study was that intra-arterial infusion chemotherapy of FCM had a good safety profile. In our study, no patient stopped treatment because of treatment-related adverse events. The most severe hematological adverse event was neutropenia, which occurred with grade 3/4 intensity in 10 (21.3%) patients. Anemia and febrile neutropenia occurred with grade 3 intensity in only one (2.1%) and two (4.3%) patients, respectively. Considering the exceptionally poor prognosis of AGC and the importance of good feasibility for AGC, the safety profile reported with FCM in our trial compares favorably with that of the same regimen of traditional i.v. chemotherapy, as reported earlier [12–15]. For example, neutropenia occurred with grade 3/4 intensity in 44% patients, which was reported by Kikuyama *et al.* [13].

In conclusion, intra-arterial infusion chemotherapy of FCM is a tolerated treatment modality with promising activity in patients with previously untreated AGC. This promising combination regimen overcomes the issues of poor tolerability and inconvenience associated with other regimens or the same regimen of traditional i.v. chemotherapy currently used in AGC.

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