Phase II study of oxaliplatin in combination with continuous infusion of 5-fluorouracil/leucovorin as first-line chemotherapy in patients with advanced gastric cancer

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This study was designed to determine the efficacy and safety of biweekly oxaliplatin in combination with infusional 5-fluouracil (5-FU) and leucovorin in patients with advanced gastric cancer (AGC). Fifty-five eligible patients with measurable or assessable M/AGC (median age 62 and 90% of patients presented with metastasis) received oxaliplatin (85 mg/m^2) intravenous infusion for 2 h, followed by intravenous infusion of 5-FU (3000 mg/m^2) and leucovorin (100 mg/m^2) for 46 h every 14 days until the patient's disease was either in progression, unacceptable toxicity, patient's withdrawal or the investigators' decision to discontinue treatment. Of the 55 enrolled patients, 48 were evaluable for response. Three patients (5.4%) showed complete remission and 20 patients (36.4%) achieved partial response. The overall response rate was 47.9%. Nineteen patients (34.5%) had stable disease and six patients (10.9%) showed progressive disease. The median time to progression was 5.6 months and the median overall survival was 10.8 months. Grade 3/4 toxicities included leucopenia (12.7%), thrombocytopenia (5.4%), diarrhoea (3.6%) and vomiting (9.1%). Peripheral neuropathy was noted in 61.8% of the patients (grade 1/2: 54.5%; grade 3: 7.3%). Our study confirmed that the combination of oxaliplatin and continuous infusion of 5-FU/leucoverin without bolus 5-FU as first-line chemotherapy is active for patients with AGC and relatively safe with lower haematological toxicity. *Anti-Cancer Drugs* **19:283–288**
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Introduction

Gastric cancer is one of the leading causes of cancer death worldwide. In Taiwan, gastric cancer, which ranks fourth in cancer-related mortality among the major types of cancer malignancies, is responsible for approximately 2400 deaths per year [1]. Complete resection is the only curative therapy for gastric cancer. Recurrent tumours are observed in up to one half of patients treated by curative intention using standardized surgical techniques. With most cases diagnosed at an advanced stage, the prognosis for this disease is extremely poor.

Randomized trials have demonstrated that 5-fluorouracil (5-FU)-based chemotherapy may improve survival and quality of life in patients with advanced gastric cancer (AGC) when compared with best supportive care [2–4]. Response rates (RRs) of approximately 20%, with manageable toxicity [5], and overall survival (OS) of 5–7 months [6,7], have been reported for 5-FU monotherapy. Combination therapy including leucovorin generally enhances the efficacy (22–48% overall RR) and has resulted in some complete responses [8–13].

Other combination regimens with cisplatin have been widely used [e.g. etoposide, doxorubicin and cisplatin; epirubicin, cisplatin and 5-FU (ECF); cisplatin, epirubicin, leucovorin and 5-FU] in patients with AGC [14,15]. These regimens yielded RRs of up to 51% but were associated with significant toxicities and patient discomfort.

Oxaliplatin is a platinum derivative which has been used along with 5-FU to treat advanced colorectal cancer [16]. It is a third-generation diaminocyclohexane platinum compound that yields a RR of 10% in single use for patients resistant to 5-FU [17,18] and of 36–58% in combination therapy (with 5-FU with or without leucovorin) [19–22]. Oxaliplatin has a dose-limiting toxicity of cumulative short-term sensory peripheral neuropathy and has been reported to inhibit the growth of five human gastric cancer cell lines. A pilot study for preoperative administration of oxaliplatin to patients with advanced scirrhous-type gastric cancer showed a clinical response and significant platinum concentration in the surgical resection tissue [23].

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A phase II study of oxaliplatin/5-FU/folinic acid (FOLFOX 6) in advanced or metastatic gastric carcinoma patients has demonstrated a good safety and efficacy rate [24]. Two further phase II studies with one investigating a regimen with reduced dosage (85 vs. 100 mg/m^2) of oxaliplatin [25], infusional 5-FU without the bolus 5-FU, and the other one using the FOLFOX 4 regimen resulted in comparable RR, time to progression (TTP) and OS [26]. The aim of this study was to evaluate the efficacy and toxicity of intravenous infusion of oxaliplatin (85 mg/m^2) over 2 h, followed by a combination of continuous infusion of 5-FU (3000 mg/m^2) and leucovorin (100 mg/m^2) over 46 h in the treatment of AGC in Taiwan.

Methods

Eligibility

Patients with histologically confirmed, nonresectable locally advanced or metastatic adenocarcinoma of the stomach were eligible if they met the following criteria: at least one lesion of ≥ 20 mm measured (in at least one dimension) by conventional techniques or ≥ 10 mm measured by spiral computed tomography (CT) scan; WHO performance status ≤ 2; aged ≥ 20 years; life expectancy ≥ 3 months; no concurrent uncontrolled medical illness or other malignancies (with the exception of curatively treated nonmelanoma skin cancer or cervical carcinoma *in situ*); adequate hepatic, renal, and bone marrow function; and serum triglyceride level ≥ 70 mg/dl. Patients were excluded from the study if they: had prior exposure to systemic chemotherapy for AGC (with the exception of adjuvant chemotherapy completed more than 6 months before study entry); were experiencing any grade of peripheral neuropathy by the National Cancer Institute Common Toxicity Criteria (NCI-CTC); or were pregnant or breast feeding. Patients were asked to give informed consent before they were enrolled in the study, which was approved by the local Ethics Committees of participating centres.

Treatment and toxicity assessment

Oxaliplatin (85 mg/m^2) (manufacture by TTY Co., Taipei, Taiwan) was given as a 2-h intravenous infusion, followed by 5-FU (3000 mg/m^2) and leucovorin (100 mg/m^2) as a continuous infusion over 46 h. Cycles were repeated every 2 weeks. Chemotherapy was given in an outpatient setting using an ambulatory pump for infusion of 5-FU and leucovorin. Antiemetic prophylaxis (granisetron with corticosteroids) was routinely administered before the oxaliplatin infusion.

The adverse events were recorded according to the NCI-CTC (version 3.0). If patients' reported a neutrophil count (< 1500/mm^3) and platelet count ($< 100\,000$/mm^3) on day 14 of any cycle, their treatment would be delayed for up to 14 days until recovery of their bone marrow function. In the case of grade 3/4 nonhaematological toxicity, treatment would be delayed up to 6 weeks until recovery. If recovery did not occur within this time period, treatment would be discontinued. In patients with neurological toxicity (paraesthesia with pain or functional impairment or symptoms) lasted more than 14 days, oxaliplatin would be modified first to 70 mg/m^2, then to 55 mg/m^2 upon recurrence, and treatment would be discontinued if neurotoxicity recurred again. If patients had grade greater than 2 of nonhaematological CTC toxicity (excluding neurological and nausea/vomiting) during the treatment period, 5-FU would be reduced to 2500 mg/m^2 upon recovery, then to 2000 mg/m^2 upon recurrence. The 5-FU would be discontinued if further recurrence of the above nonhaematological toxicity occurred. In the event of more severe haematological toxicity (i.e. neutrophil count < 500/mm^3, neutrophil count < 1000/mm^3 with fever, or platelet count $< 50\,000$/mm^3) or if the delayed treatment did not recover within 2 weeks, the oxaliplatin would be modified first to 70 mg/m^2, then to 55 mg/m^2 upon recurrence, and treatment would be discontinued if further recurrence occurred.

Study end points

Four weeks before the treatments began, CT scans of measurable lesions were performed. Baseline laboratory examinations were recorded at the screening visit: haematology (white blood cell count, red blood cell count, haemoglobin, haematocrit, and platelet count); biochemistry (total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, potassium, sodium, and creatinine); and electrocardiogram. Haematology and biochemistry examinations were performed at each scheduled visit. Tumour responses were evaluated on the basis of RECIST criteria. Complete response was defined as the disappearance of all target lesions; partial response (PR) as at least a 30% decrease in the sum of the longest diameter of target lesions (compared with baseline); progressive disease as at least a 20% increase in the sum of the longest diameter of target lesions (compared with the smallest sum recorded since treatment started or the appearance of new lesions); and stable disease as small changes that did not meet the previous criteria. The responses were confirmed by subsequent CT 4 weeks after the initial response documentation. Treatment was continued until disease progression, unacceptable toxicity, patient's withdrawal or the investigators' decision to discontinue treatment. Patients were considered assessable for response if they had early disease progression or had received at least four cycles of treatment with at least one tumor assessment. Patients who discontinued the study were evaluated at least every 3 months for survival status. The primary end point of the study was the overall RR and the secondary end points were toxicities, duration of response, evaluation of TTP, and OS.

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The number of patients required for this phase II study was calculated according to the two-stage optimal design of Simon [27]. As more than five patient responses were observed out of the first 15 patients, an additional 31 patients were recruited. The regimen was considered active if more than 18 responses among 46 evaluable patients were obtained. Descriptive statistics [point estimates and 95% confidence intervals (CIs)] were used to analyse the overall RR. Duration of response, TTP, and OS were evaluated by the Kaplan–Meier method.

Results

Patient characteristics

From April 2003 to December 2004, 55 patients (42 men, 13 women) were enrolled in the study. Patient's characteristics were listed in Table 1. The median age was 62 years (range: 27–78 years); 42 patients had PS 0 or 1. At baseline there were 23 (42.6%) patients with abnormal ECG results, four (7.3%) of which were clinically significant. Prior surgery for gastric adenocarcinoma had been performed on 28 (50.9%) patients, 10 patients (18.2%) had prior adjuvant chemotherapy (at least 6 months before the start of study medication) after surgery, and one patient (1.8%) had prior radiotherapy. During the course of the study, 42 patients had measurable metastatic lesions. The most common sites of metastases were the lymph nodes.

Table 1 Patient characteristics

	No. of patients	%
Sex		
Male	42	76
Female	13	24
Age (years)		
Median (interquartile range)	62 (14)	
Range	27–78	
Performance status		
0	13	23.6
1	29	52.7
2	13	23.6
Disease status		
Locally advanced	5	9.1
Metastatic	50	90.9
Newly diagonized	28	51
Recurrent	27	49
Surgical history for gastric adenocarcinoma		
Previous history of primary surgery	28	51
No history of any surgery	27	49
Adjuvant chemotherapy		
No	45	81.8
Yes	10	18.2
No. of organs involved in metastatic disease		
0	2	3.6
1	20	36.4
2	21	38.2
3	12	21.8
Organs most commonly involved		
Ascites	10	18.2
Liver	29	52.7
Nodes	37	67.3
Pleura	5	9.1
Lung	5	9.1

Tumour response

Of the first 15 patients recruited to the study, eight were responders. The response to treatment was not evaluated in seven of the intent-to-treat population because of withdrawal from the study before completing 8 weeks (four cycles) of treatment. Fifty-five patients were evaluated for response assessment, including one patient with confirmed early disease progression. Three patients (5.4%) achieved complete remission and 20 patients (36.4%) showed a PR, yielding an overall RR of 41.8% (95% CI: 33.3–62.8). Stable disease was observed in 19 patients (34.5%), and six patients (10.9%) showed progressive disease. Of the 55 patients evaluated, seven patients (12.7%) were not evaluable. No secondary surgical approaches for those patients who had responded or who had initially only advanced disease.

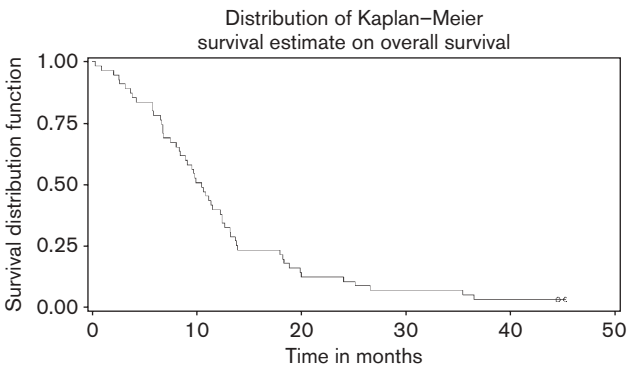
Survival

Of the 23 patients who had a complete or PR, nine were followed to a confirmed date of progression. A median duration of response was 4.9 months for that subpopulation. During follow-up, 23 of the evaluable patients had documented disease progression, and the median TTP was 5.6 months. At the last date of assessment, 21 patients in the evaluable population were alive and 27 had died. Further update of the assessment showed that two patients in the evaluable population were alive and 46 had died. The median OS was 10.4 months (95% CI: 9.2–13.4) as shown in Fig. 1.

Toxicity and adverse events

A total of 457 chemotherapy cycles were administered, with a median of eight cycles per patient (range: 1–27). Less than 30% of patients received more than 10 cycles. For the ITT population ($n = 55$), the mean doses of oxaliplatin, 5-FU, and leucovorin were 82.6, 2938, and

Fig. 1



Kaplan–Meier curve for overall survival in 55 ITT patients. Two patients in the evaluable population were alive and 46 had died. The median overall survival duration was 10.4 months (95% CI: 9.2–13.4). CI, confidence interval.

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100 mg/m^2, respectively. The most common reason for dose reduction was thrombocytopenia.

The toxicity profile is summarized in Table 2. The common toxicities were leucopenia (74.5%), neutropnia (63.6%), thrombocytopenia (72.7%), vomiting (69.1%), and anaemia (83.6%). Grades 3 and 4 haematological toxicities included leucopenia in seven patients (12.7%), neutropenia in 12 patients (21.8%), and thrombocytopenia in three patients (5.5%). Neurotoxicity was noted in 34 patients (61.8%), with grade 3 reported in four patients (7.3%), and no patients classified as grade 4. Grade 4 toxicities were reported infrequently: thrombocytopenia one (1.8%), vomiting one (1.8%), fever one (1.8%), and infection one (1.8%). No patients discontinued treatment because of treatment-related adverse effects.

A total of 839 treatment-related adverse events were reported in the ITT population. The most frequently reported adverse events were associated with the digestive system (94.5%), haematological system (90.9%), metabolic and nutritional disorders (85.5%), the nervous system (85.5%), and the body as a whole (80.0%). Events experienced by more than half the ITT population included leucopenia (81.8%), neutropenia (63.6%), thrombocytopenia (72.7%), vomiting (63.6%), nausea (61.8%), anaemia (58.2%), and diarrhoea (50.9%). About half of adverse events were grade 1 (51.7%), 28.8% were grade 2, 15.0% were grade 3, and 3.1% were grade 4.

Discussion

Patients with locally advanced or metastatic carcinoma of the stomach may benefit from palliative chemotherapy [2–8]. The combination of cisplatin and 5-FU has been considered an active regimen for the treatment of AGC. Oxaliplatin is a platinum derivative proven to have a more efficacious and less toxic activity than cisplatin in some literature [6,16–20]. It was usually used in the combination of 5-FU and leucovorin to treat gastrointestinal malignancy [17–20,24,25].

Our study has resulted in a similar efficacy profile compared with the previously reported phase II trials of the oxaliplatin/leucovorin/5-FU regimen (with different doses and schedules) in patients with locally advanced or metastatic gastric carcinoma (Table 3) [23–26]. The RR derived from our study (41.8%) was similar to those of earlier studies (38–45%). The median TTP in our study was 5.6 months, at the low end of the range for the other studies (5.6–7.1 months). Whether it was related to the metastatic status of disease in the initial enrollment in 42 of our 48 evaluable patients is still unknown. The median OS of 10.4 months was the highest for those patients receiving first-line chemotherapy only (8.6–9.6 months) [24–26].

The level of grade 3 peripheral neuropathy (7%) reported in our study was similar to that found in the study by De Vita *et al.* (5%) [26]. Grade 1/2 neuropathy, however, was relatively higher (55%) in this study, which may be related to the relatively higher number of chemotherapy cycles administered (8 vs. 7) and, therefore, the higher cumulative dosage of oxaliplatin compared with the previous phase II study conducted by De Vita *et al.* [26]. The study by Louvet *et al.* [24] incorporated a higher biweekly dose of oxaliplatin (100 mg/m^2 vs. 85 mg/m^2) with the administration of median 10 cycles of chemotherapy, which resulted in higher rates of incidences of grade 1/2 neurotoxicity (66%) and grade 3 neurotoxicity (21%), compared with that of this study. The grade 3/4 haematological toxicities were moderate, with 13, 21.8, and 5% of patients experiencing leucopenia, neutropenia, and thrombocytopenia, respectively. The haematological toxicities in this study were relatively milder than the previous phase II studies using the bolus 5-FU containing FOLFOX regimens [24,26]. One phase

Table 2 Incidence of treatment-related toxicities (NCI-CTC scale, version 3.0)

Toxicity	Total incidence (%)	Grade				
		1	2	3	4	≥ 3
Haematological						
Leucopenia	41 (74.5)	10 (18.2)	24 (43.6)	7 (12.7)	0 (0.0)	7 (12.7)
Neutropenia	35 (63.6)	17 (30.9)	6 (10.9)	7 (12.7)	5 (9.1)	12 (21.8)
Thrombocytopenia	40 (72.7)	30 (54.5)	7 (12.7)	2 (3.6)	1 (1.8)	3 (5.5)
Anemia	46 (83.6)	11 (20.0)	24 (43.6)	11 (20.0)	0 (0.0)	11 (20.0)
Gastrointestinal						
Nausea	34 (61.8)	21 (38.2)	11 (20.0)	2 (3.6)	0 (0.0)	2 (3.6)
Vomiting	38 (69.1)	17 (30.9)	16 (29.1)	4 (7.3)	1 (1.8)	5 (9.1)
Diarrhoea	30 (54.5)	17 (30.9)	11 (20.0)	2 (3.6)	0 (0.0)	2 (3.6)
Neurosensory[a]	34 (61.8)	16 (29.1)	14 (25.5)	4 (7.3)	0 (0.0)	4 (7.3)
Others						
Fever	13 (23.6)	10 (18.2)	1 (1.8)	1 (1.8)	1 (1.8)	2 (3.6)
Infection	21 (38.2)	4 (7.3)	6 (10.9)	10 (18.2)	1 (1.8)	11 (20.0)
Cutaneous	19 (34.5)	14 (25.5)	3 (5.5)	2 (3.6)	0 (0.0)	2 (3.6)

NCI-CTC, National Cancer Institute Common Toxicity Criteria.
[a]According to an oxaliplatin-specific scale (grades 0–3).

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Table 3 Summary and comparing the efficacy and toxicity of different 5-fluorouracil/leucovorin (folinic acid)/oxaliplatin (FLO) regimen as first-line chemotherapy in AGC patients

Study	No. of evaluable patients	% RR (% CR)	Median TTP (months)	Median OS (months)	FLO study regimen (mg/m^2)	Median no. of cycles (range)	Grade 3/4 toxicities (%)	Grade 1/2 neurotoxicities[a] (%)	Grade 3 neurotoxicity[a] (%)
Louvet *et al.* [24]	49	45 (4)	6.2	8.6	400 (bolus) + 3000 (continuous infusion)/400/100	10 (1–17)	Neutropenia (38) Leucopenia (19) Anemia (11)	66	21
Al-Batran *et al.* [25]	37	43 (3)	5.6	9.6	2600 (continuous infusion)/500/85	7 (1–17)	Anemia (7) Diarrhoea (7) Neutropenia (5)	39	0
De Vita *et al.* [26]	61	38 (7)	7.14	11.2[b]	400 (bolus) + 1200 (continuous infusion)/200/85	7 (3–15)	Neutropenia (36) Leucopenia (16) Anemia (10)	26	5
Hwang *et al.* (this study)	48	48 (6)	5.6	10.8	3000 (continuous infusion)/100/85	8 (1–27)	Leucopenia (13) Thrombocytopenia (6) Anemia (20)	55	7

[a]According to an oxaliplatin-specific scale (grades 0–3).
[b]Including OS of 9.46 months in 25 patients who received first-line therapy followed by supportive care and OS of 12.74 months in 36 patients who received second-line chemotherapy.
AGC, advanced gastric cancer; CR, complete response; FLO, 5-fluorouracil/leucovorin/oxaliplatin; OS, overall survival; RR, response rate; TTP, time to progression.

II study by Chen [29] using oral flouropyrimidine UFT also showed less incidence of neutropenia. The purpose of eliminating the bolus 5-FU in this study was not only to decrease the incidence of leucopenia, neutropenia, and thrombocytopenia, but also to simplify the treatment procedure in clinical practice. Other grade 3/4 toxicities reported in our study included anaemia (20%), nausea (4%), vomiting (9%), and diarrhoea (4%).

One phase II study using weekly oxaliplatin of 50 mg/m^2 without the bolus 5-FU showed favourable haematological toxicities with grade 3/4 neutropenia of only 8%. Grade 3 neuropathy was absent. The median TTP and OS were 6.5 and 11.4 months, respectively [28], which was comparable with that of this study. Therefore, weekly lower dosage of oxaliplatin-based regimen could be considered in the future. Another recent phase II study using modified FOLFOX 4 regimen with a low dose of leucovorin of 20 mg/m^2 showed a good safety profile, and again the median TTP and OS were also close to that of our study with TTP of 7.7 months and OS of 11.2 months [29]. A recent study used weekly lower dosage of oxaliplatin of 70 mg/mg^2, combining oral fluoropyrimidines administered in a chronomodulated fashion in treating advanced colorectal cancer patients, showed an excellent toxicity profile both in terms of neuropathy and haematological toxicities. The efficacies in terms of median TTP and OS were superior than the earlier studies of advanced colorectal cancer [30]. This could be an interesting regimen that could probably be used in treating advanced/metastatic gastric cancer. Therefore, further studies could be focused on using oral fluoropyrimidines such as tegafur–uracil instead of infusional fluorouracil in treating advanced/metastatic gastric cancer.

Two phase III studies have proven the efficacy and the manageable toxicities of oxaliplatin-based regimens compared with cisplatin-based regimen. One study by Al-Batran *et al.*, in which the regimen used [oxaliplatin (85 mg/m^2), infusional 5-FU (2600 mg/m^2), FA (200 mg/m^2)] was similar to that of this study, demonstrated similar efficacy in terms of overall RR (34%) and TTP (5.7 months). The incidence of grade 3/4 leukopenia, neutropenia, and thrombocytopenia was also low (< 10%) [31]. The phase III REAL-2 study used oral fluoropyrimidines capecitabine instead of infusional 5-FU also showed equivalent efficacy in terms of overall RR (47.9%), TTP (7.0 months), and OS (11.2 months). The safety profile in terms of haematological toxicity was also similar to that of this study with grade 3/4 leukopenia (13.8%), neutropenia (27.6%), and thrombocytopenia (5.2%) [32]. Therefore, the results of the two phase III studies confirmed the results of our study.

In conclusion, our study confirms that the combination of oxaliplatin and continuous infusion of 5-FU/leucoverin without bolus portion of 5-FU as first-line chemotherapy is active for patients with AGC and relatively safe with lower haematological toxicity. Our study suggests that using a simpler treatment regimen, in which oxaliplatin administered as a 2 h infusion, followed by leucovorin and 5-FU coadministered as a 46-h infusion, may give a comparable efficacy and tolerable toxicity to AGC patients.

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