Phase I dose escalation study of oxaliplatin combined with oral tegafur–uracil and leucovorin in patients with advanced gastric cancer

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Our aim was to determine the dose-limiting toxicities (DLTs), maximum tolerated dose (MTD) and recommended dose of oxaliplatin combined with oral tegafur–uracil and leucovorin. Twenty-eight chemo-naïve patients with advanced gastric cancer were enrolled. Oxaliplatin (55, 70, 85, 100 and 115 mg/m^2) was given as a 2-h infusion on days 1 and 15. Oral tegafur–uracil (300 mg/m^2 per day) and leucovorin (60 mg/day) were given 3 times a day from days 1 to 21 (28-day cycle). DLTs were defined as grade IV hematologic toxicity or grade III non-hematologic toxicity. The MTD for oxaliplatin was 100 mg/m^2. The most common DLT was diarrhea. Major grade III/IV toxicities included vomiting, diarrhea, renal dysfunction, leukopenia and thrombocytopenia. There were two treatment-related deaths. Intent-to-treat response was graded as partial response in 13 patients (46.4%; 95% confidence interval 26.74–66.12%), stable disease in nine and disease progression in five. As of June 2004, 17 patients had died. The median time to treatment failure, time to progression and overall survival were 124, 308 and 434 days, respectively. The recommended dose for the phase II study is oxaliplatin 100 mg/m^2 biweekly with oral tegafur–uracil (300 mg/m^2 per day) and leucovorin (60 mg/day) 3 times a day for 21 days. *Anti-Cancer Drugs* 16:47–51 © 2005 Lippincott Williams & Wilkins.

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Introduction

Gastric adenocarcinoma is a common type of cancer and cause of death in Taiwan [1] and in the world, generally [2]. Most patients receive curative surgical resection; however, many patients relapse with local-regional recurrence or distant metastases [3]. Approximately, 20–30% of patients present with inoperable disease at diagnosis. Thus, the majority of patients need palliative treatment at some point [4]. Currently, there are no standard combination regimens for advanced gastric cancer [5]. Nevertheless, 5-fluorouracil (5-FU)-based regimens are used for conventional therapy in current clinical practice. Randomized trials have demonstrated that 5-FU-based chemotherapeutic regimens may improve survival and quality of life in patients with advanced gastric cancer as compared to best supportive care [6].

Tegafur–uracil (uracil combined with tegafur at a **4:1** ratio) is a second-generation, oral 5-FU prodrug. Uracil prevents degradation of 5-FU by inhibiting dehydropyrimidine dihydrogenase (DPD), and this leads to increased concentrations of 5-FU in the plasma and tumor tissue [7]. Tegafur–uracil, which is widely available in Asia, has been approved for use in Taiwan in the treatment of metastatic colorectal, gastric and breast cancer. Prolonged administration of tegafur–uracil results in a similar or higher maximum concentration achieved (C_{max}) and area under the curve (AUC) as compared to continuous infusion of 5-FU; however, the pharmacokinetic patterns are different [8,9]. Phase II data suggest that tegafur–uracil and 5-FU have similar activity against gastric cancer [10]. Patient tolerability to tegafur–uracil on a 28-day on and 7-day off schedule has been excellent. Common toxicities include anorexia, nausea and vomiting, and diarrhea. Hematologic toxicity is rare.

Oxaliplatin (OXA), a cytotoxic agent from the diaminocyclohexane platinum family, has a mechanism of action similar to that of other platinum derivatives, but its

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spectrum of antitumor activity against tumor models differs from those of cisplatin and carboplatin [11]. Activity against cisplatin-resistant colon carcinoma cell lines and the synergistic activity of the OXA and 5-FU combination have been shown experimentally [11]. OXA clinical toxicity is distinct from other platinum drugs: it has no renal toxicity, and it causes both a reversible acute, cold-related dysesthesia and a dose-limiting cumulative peripheral sensory neuropathy [12]. Its activity as a single agent in patients with metastatic colorectal cancer either previously untreated or treated with 5-FU was demonstrated in phase II trials; response rates ranged from 10 to 24% [13,14]. Clinical evidence also supports the combination of 5-FU, leucovorin (LV) and OXA [15].

In a pilot study, patients with advanced scirrhous-type gastric cancer were given OXA preoperatively; the patients had a clinical response and the platinum concentration in the postoperative tissue was significant [16]. OXA combined with oral tegafur–uracil and LV has synergistic antitumor activity against human colorectal HT29 cell xenografts in athymic nude mice [17]. No data have been collected from phase I and II clinical studies on the use of the OXA plus oral tegafur–uracil and LV combination in patients with colon cancer or gastric cancer. This advantage of combination does not require hydration for OXA and tegafur–uracil/LV can be given orally in an outpatient setting. Our primary objective for this study is to determine the dose-limiting toxicities (DLTs) and the recommended dose of OXA, in combination with a fixed dose of oral tegafur–uracil and LV in patients with advanced gastric cancer. These data will be applied to a future phase II study. The secondary end points are the response rate, safety profiles, time to progression and overall survival.

Patients and methods

Inclusion criteria

The inclusion criteria included histologic or cytologic documentation of gastric adenocarcinoma, metastatic disease, no history of palliative chemotherapy, presence of at least one measurable lesion and age 18–75 years. Measurable lesions were defined as those lesions that could be measured in at least one dimension as ≥ 20 mm with conventional techniques or ≥ 10 mm with spiral computed tomography (CT). Previously irradiated lesions were not considered as measurable target lesions. Other criteria included an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2, absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN), total bilirubin $\leq 1.5 \times$ ULN, and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN ($\leq 5.0 \times$ ULN with hepatic metastasis).

Patients must have recovered from the effects of recent surgery (at least 2 weeks apart) and radiotherapy (at least 4 weeks apart). Patients with previous adjuvant or neoadjuvant chemotherapy were included if they had not been treated for more than 6 months between the end of adjuvant chemotherapy and first relapse. Patients could complete the initial work-up within 2 weeks of the first therapy for imaging studies, and within 14 days of the first therapy for clinical evaluation and biological work-up. CT scans and radiographs were mandatory for disease assessment. Imaging studies were conducted every 2 months. Complete blood count was checked before each OXA infusion. Biochemical analyses were performed every month.

All patients must sign informed consent before beginning of the protocol procedure. This study was approved by the Scientific and Research Ethics Committees of the participating institutions.

Ineligibility criteria

Patients with the following were excluded: life expectancy < 3 months; central nervous system (CNS) metastasis (including clinical suspicion); bone metastasis only; pregnancy or breast-feeding; clinically detectable peripheral neuropathy > 2 on the Oxaliplatin Specific Neurological Scale; concomitant illness that might be aggravated by chemotherapy; active cardiac disease (e.g. angina or myocardial disease) within the 6-month period preceding entry into the study; active infection and history of other malignancy, except curatively treated non-melanoma skin cancer or cervical carcinoma *in situ*; unfit mental status; hypersensitivity to any component of the chemotherapeutic regimen; intestinal obstruction, malabsorption or any condition that would prevent oral intake of the study drugs.

Treatment schedule

OXA was given on day 1 and day 15 as a 2-h infusion. A fixed dose of oral tegafur–uracil (300 mg/m^2/day) and leucovorin (LV 60 mg/day) was given 3 times a day from day 1 to day 21, followed by a 7-day break. Anti-emetics with serotonin (5-HT$_3$) receptor antagonist activity and steroids were given before OXA infusion. Treatment was continued until the disease progressed. Treatment was ended if unacceptable toxicity occurred, the patient refused to continue or further treatment was needed. Patients who maintained a response or stable disease after stopping OXA took oral tegafur–uracil/uracil until the disease progressed. OXA (Oxalip) and tegafur–uracil 300 (UFUR) were obtained from TTY Biopharm (Taipei, Taiwan).

Toxicities and identification of DLTs

Toxicities were graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC,

version 2, 1998), except peripheral-sensitive neuropathy which was graded according to a WHO modified specific grading system (grade 1 = short-term paraesthesia, with complete regression before next cycle; grade 2 = persistent paraesthesia/dysesthesia between two cycles without functional impairment; grade 3 = permanent functional impairment) [18]. The following toxicities were defined as DLT if they occurred during the first cycle of treatment: ANC < 500/ml or platelets $< 50\,000$/ml for more than 5 days; ANC < 500/ml with fever requiring parenteral antibiotics; non-hematologic toxicity of NCI CTC grade III, except alopecia; and grade III nausea and vomiting in the first course of treatment.

Maximum tolerated dose (MTD) and dose escalation

OXA doses of 55, 70, 85, 100 and 115 mg/m^2 were used. The initial number of patients to be enrolled per dose level was 3. If none of three patients experienced DLT, the OXA dose was escalated to the next level. If one of three patients had DLT, three more patients were enrolled at this dose level. If at least two of three or at least two of six patients had DLT, the dose was not escalated. This dose was defined as the MTD. The recommended dose of oxaliplatin for phase II is defined at highest dose level at which less than two of six patients experience DLT.

Response evaluation and statistical methods

Patients were evaluated every two courses for therapy. Tumor responses were determined according to the Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines [19]. The time to disease progression from date of starting chemotherapy and the overall survival from date of starting chemotherapy to death from any cause were examined using the Kaplan–Meier method.

Results

Patient characteristics

We enrolled 28 chemo-naïve patients from three hospitals in this study between October 2001 and August 2003 (Table 1).

Table 1 Characteristics of the patients in the study population ($n = 28$)

Characteristics	No. patients
Chang Gung Memorial Hospital	
Taipei	18
Keelung	9
Kaohsing	1
Gender (female/male)	11/17 (39.3%/60.7%)
Age (years) [median (range)]	58.5 (37–72)
Performance status	
0	2
1	22
2	4
Primary tumor location	
cardia	3
cardia and body	3
body	7
body and antrum	7
antrum	3
stump cancer	2
unclassified	3
Disease involvement sites	
local-regional	4
liver	9
peritoneal	8
intra-abdominal lymph nodes	10
ovary	2
adrenal	1
abdominal wall	2
lung	1
No. of organs involved	
1	18
2	8
3	1
4	1

Table 2 DLTs for each dose level

Dose of oxaliplatin (mg/m^2)	No. patients	Diarrhea	Fatigue	Leukopenia and neutropenia	Gastrointestinal bleeding
55	7		1		
70	6			1 (death)	
85	6	1			
100	6				1 (death)
115	3	2			
Total	28	3	1	1	1

DLTs and MTD

The incidence of DLT during oxaliplatin dose escalation is demonstrated in Table 2. In the dose I group, one patient had grade III fatigue in the first cohort of three patients. Three more patients were enrolled in the dose I group. Because one patient's disease progressed rapidly in the first course, we could not evaluate toxicity; therefore, seven patients were included in the dose I group. One patient died of grade IV leukopenia with infection in the first cohort of three patients at dose II, but no obvious adverse effects were noted in three other patients. A patient had grade IV diarrhea in the first cohort of three patients at dose III. At dose IV, one patient died of gastrointestinal bleeding in the first cohort of three patients. Two patients had grade IV diarrhea in the first cohort of three patients at a dose of OXA 115 mg/m^2. Therefore, the MTD of OXA was 100 mg/m^2 on day 1 and day 15 when it was given with tegafur–uracil 300 mg/m^2 and LV 60 mg (3 times a day for 21 days on a 28-day cycle).

Safety profile

The study population completed 138.5 treatment cycles, with a mean of 4.9 per patient (range 0.5–23.5). The maximum treatment-related clinical adverse events of all patients are shown in Table 3. The overall toxicities were quite acceptable. The most common grade III/IV toxicities were diarrhea (four patients, 14.3%), vomiting (four, 14.3%), thrombocytopenia (two, 7.1%) and renal dysfunction (two, 7.1%). There were two treatment-related deaths.

Table 3 Overall treatment-related clinical adverse events and maximum toxicity according to NCI-CTC criteria (version 2.0, 1998), *n* = 28

	Grade [*n* (%)]				
	1	2	3	4	5
Leukopenia	7 (25)	3 (10.7)	0	0	1[a] (3.6)
Neutropenia	3 (10.7)	3 (10.7)	0	0	1[a] (3.6)
Anemia	5 (17.9)	13 (46.4)	2 (7.1)	0	0
Thrombocytopenia	9 (32.1)	6 (21.4)	2 (7.1)	0	0
Hemorrhage, GI	0	0	0	0	1 (3.6)
Nausea	7 (25.0)	4 (14.3)	0	0	0
Vomiting	3 (10.7)	5 (17.9)	4 (14.3)	0	0
Diarrhea	3 (10.7)	4 (14.3)	4 (14.3)	0	0
Mucositis	3 (10.7)	1 (3.6)	0	0	0
Abdominal pain	3 (10.7)	2 (7.1)	0	0	0
Numbness[b]	4 (14.3)	2 (7.1)	0	0	0
Cold paraesthesia	6 (21.4)	2 (7.1)	0	0	0
Dizziness	4 (14.3)	0	0	0	0
Fatigue	3 (10.7)	0	1 (3.6)	0	0
Insomnia	5 (17.9)	2 (7.1)	0	0	0
Renal	1 (3.6)	0	2 (7.1)	0	0
Liver (ALT/AST)	7 (25)	2 (7.1)	0	1 (3.6)	0
Hypernatremia	2 (7.1)	0	0	0	0
Hyponatremia	0	0	1 (3.6)	0	0
Hypokalemia	5 (17.9)	1 (3.6)	0	0	0

[a]Same patient.
[b]Oxaliplatin Specific Neurological Scale [18].

Efficacy, follow-up and survival

Intent-to-treat responses in 28 patients were evaluated by RECIST as partial response in 13 patients (46.4%; 95% confidence interval 26.74–66.12%), stable disease in nine (32.1%) and disease progression in five (17.9%). One patient withdrew early from the study and could not be evaluated for response due to DLT in dose level I.

By the end of June 2004, 10 patients were still alive, one patient was lost to follow-up and 17 patients had died. The median time to disease progression was 308 days and the median time to treatment failure was 124 days. Overall survival was 434 days. The reasons for removal from the trial included adverse events in 17 patients (prolonged low platelet count of $75–100 \times 10^9$/l in nine, numbness in three, fatigue in one, infection in three and gastrointestinal bleeding in one), disease progression in eight patients, investigator recommendation in two patients and refusal of further treatment by one patient.

Discussion

The MTD of OXA was 100 mg/m^2 when it was given biweekly with oral tegafur–uracil (300 mg/m^2) and LV (60 mg) 3 times per day for 21 days. A 7-day rest was allowed between treatments. The most common DLT was diarrhea. This combination is feasible and can be easily applied in an outpatient setting as a first-line therapy for advanced gastric cancer. The toxicity is acceptable. Douillard *et al.* [20] gave OXA 130 mg/m^2 every 3 weeks with oral tegafur–uracil 300 mg/m^2 and LV 90 mg for 14 days on a 21-day schedule as first-line therapy for patients with advanced colorectal cancer. The major grade III/IV toxicities in 64 patients were diarrhea in 11%, nausea or vomiting in 14%, sensory neuropathy in 15%, asthenia in 11% and neutropenia in 10%; no patients developed febrile neutropenia. The toxicity profiles were quite similar to those in our study. The major reasons for removal of patients from our trial were a prolonged low platelet count of $75–100 \times 10^9$/l in nine patients. Therefore, we modified this protocol so that OXA could still be used if a patient's platelet count decreased from 100 to 75×10^9/l in our future phase II study.

The use of OXA with capecitabine (Xeloda), another oral 5-FU prodrug, has been reported previously. Zeuli *et al.* [21] gave OXA 120 mg/m^2 every 3 weeks with capecitabine 2500 mg/m^2/day for 2 weeks and then allowed 1 week of rest. The major DLT was diarrhea. Díaz-Rubio *et al.* [22] reported that the MTD of OXA was 130 mg/m^2 when it was given as a 2-h infusion on day 1 with oral capecitabine 1000 mg/m^2 twice daily for 14 days, followed by a 7-day rest. The DLTs were diarrhea and thrombocytopenia. From these reports and present study, OXA with oral 5-FU prodrugs is feasible and has acceptable responses.

The combination of OXA and infusional 5-FU plus LV is active and comparatively safe. It should be considered as a standard therapy for patients with advanced colorectal cancer [23,24]. In addition, biweekly OXA and infusional 5-FU plus LV is active and well tolerated in patients with advanced gastric cancer [25,26]. Response rates, time to progression and overall survival were comparable to those achieved with other combination chemotherapy regimens, with significantly less toxicity. However, infusional 5-FU and LV requires a central catheter or costly infusion pump. An oral formulation of 5-FU would allow for prolonged exposure to 5-FU without a central catheter or infusion pump. The response rate among our 28 patients was 46.4%. The time to progression and overall survival were similar to those for OXA and infusional 5-FU and LV in patients with advanced gastric cancer [25,26]. The combination of OXA and oral 5-FU prodrugs plus LV may be as effective and more convenient than OXA with infusional 5-FU and LV in patients with advanced gastric cancer.

In conclusion, the recommended dose of OXA was 100 mg/m^2 when it was given biweekly with oral tegafur–uracil (300 mg/m^2) and LV (60 mg) 3 times daily for 21 days followed by a 7-day rest. The toxicity profiles, response rate, time to progression and overall survival were acceptable for use of this regimen in our phase II study, which is ongoing.

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