Phase II study of weekly oxaliplatin and 24-h infusion of high-dose 5-fluorouracil and folinic acid in the treatment of advanced gastric cancer

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To investigate the efficacy and safety of combining weekly oxaliplatin with weekly 24-h infusion of high-dose 5-fluorouracil (5-FU) and folinic acid (FA) in treatment of patients with advanced gastric cancer; Patients with histologically confirmed, locally advanced or recurrent/metastatic gastric cancer were studied. Oxaliplatin 65 mg m⁻² 2-h intravenous infusion, and 5-FU 2600 mg m⁻² plus FA 300 mg m⁻² 24-h intravenous infusion, were given on days 1 and 8, repeated every 3 weeks. Between January 2001 through January 2002, 55 patients were enrolled. The median age was 64 years (range: 22–75). In all, 52 patients (94.5%) had recurrent or metastatic disease and three patients had locally advanced disease. Among 50 patients evaluable for tumour response, 28 patients achieved partial response, with an overall response rate of 56% (95% confidence interval (CI): 41.8–70.3%). All 55 patients were evaluated for survival and toxicities. Median time to progression and overall survival were 5.2 and 10.0 months, respectively, during median follow-up time of 24.0 months. Major grades 3–4 toxicities were neutropenia in 23 cycles (7.1%) and thrombocytopenia in 16 cycles (5.0%). Treatment was discontinued for treatment-related toxicities in nine patients (16.4%), of whom eight were due to oxaliplatin-related neurotoxicity. One patient (1.8%) died of neutropenic sepsis. This oxaliplatin-containing regimen is effective in the treatment of advanced gastric cancer. Except for neurotoxicity that often develops after prolonged use of oxaliplatin, the regimen is well tolerated.

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Gastric cancer is the second leading cause of cancer death worldwide (Ho, 1988; Roder, 2002). The prognosis is generally poor, with overall 5-year survival ranged from 5 to 15%. Most patients present with advanced or metastatic diseases, for which curative resection is not possible. Chemotherapy is used primarily for palliation of symptoms (Findlay and Cunningham, 1993; Wils, 1996; De Vivo et al, 2000). In the past three decades, a variety of chemotherapy regimens were developed for the treatment of advanced gastric cancer (MacDonald et al, 1980; Preusser et al, 1989; Wilke et al, 1990; Wils et al, 1991; Kim et al, 1993; Cocconi et al, 1994; Zaniboni et al, 1995; Ychou et al, 1996; Cheng et al, 1998). All these regimens had variable degrees of success in phase II trials; however, results of the subsequent phase III trials often failed to confirm the relatively high response rates of earlier reports (Kelsen et al, 1992; Kim et al, 1993; Cocconi et al, 1994; Webb et al, 1997; Vanhoef et al, 2000). The survival benefit was limited with overall survival consistently below 10 months, and substantial treatment-related toxicities were observed in most regimens (Waters et al, 1999; Ajanie et al, 2003; Ohtsu et al, 2003). Further, second-line chemotherapy is hardly effective in most trials, indicating the rapid emergence of drug resistance of gastric cancer cells to currently available anticancer drugs (Findlay and Cunningham, 1993; Wils, 1996; De Vivo et al, 2000). New treatments with better therapeutic index or novel agents with lesser cross-resistance are needed.

Oxaliplatin is a third-generation platinum compound that has a wide range of antitumour activities (Machover et al, 1996; Monnet et al, 1998; de Gramont et al, 2000; Misset et al, 2001). Compared with cisplatin, oxaliplatin appears to have a better safety profile; and the cross-resistance to cisplatin is minimal (Kollmannsberger et al, 2002). Oxaliplatin has higher anticancer activity than cisplatin in some preclinical experiments (Di Francesco et al, 2002). Synergism between oxaliplatin and 5-fluorouracil (5-FU) has been demonstrated in vitro (Pendyala and Creaven, 1993; Hsu et al, 2000), and in vivo (Andre et al, 1999). Combination of oxaliplatin and 5-FU has proven effective as first- or second-line treatment for advanced colorectal cancer (Machover et al, 1996; de...
PATIENTS AND METHODS

Patients

Eligibility criteria of the patients included (1) pathologically confirmed, locally advanced (nonresectable), recurrent or metastatic gastric cancer, (2) objectively measurable disease by imaging studies, (3) no prior chemotherapy except postoperative adjuvant chemotherapy that was received more than 12 months before entry into the study, (4) ECOG (Eastern Cooperative Oncology Group) performance status ≤ 2, (5) age between 18 and 75 years, (6) adequate hepatic, renal, and bone marrow functions, and (7) serum triglyceride > 70 mg dl⁻¹. The low limit for serum triglyceride was set to avoid HDFL-related hyperammonaemic encephalopathy, which occurs in around 5% of Taiwanese patients (Yeh and Cheng, 1997).

Exclusion criteria included (1) pre-existing peripheral neuropathy, (2) pregnant, breastfeeding, or woman of child-bearing potential without adequate contraception, (3) concurrent or prior malignancy except curatively resected cervical carcinoma in situ or squamous cell carcinoma of skin, (4) central nervous system metastases, (5) active infection, and (6) concurrent treatments that interfered with study evaluation. This study was approved by the ethics committee of all participating institutes. Signed informed consent was obtained from all patients.

Study design

This is a prospective, multicentre, phase II clinical trial.

Chemotherapy protocol

On days 1 and 8 of each cycle of chemotherapy, oxaliplatin 65 mg m⁻² was given as a 2-h intravenous infusion, then followed by 5-FU 2600 mg m⁻² and FA 300 mg m⁻² as a continuous 24-h intravenous infusion. Treatment was repeated every 21 days. Treatment was continued until disease progression or unacceptable toxicity developed. Patients with complete response received at least two more cycles of chemotherapy.

Dose modification

Subsequent cycle of chemotherapy was withheld if peripheral blood neutrophils < 1500 mm⁻³ or platelets < 100 000 mm⁻³ was noted on the due day. If recovery of neutrophils and platelets took more than 3 weeks after the due day, the patient was removed from protocol treatment. 5-FU was decreased to 2000 mg m⁻² for subsequent cycles if grade 4 thrombocytopenia or neutropenia developed in the preceding cycle of chemotherapy. Dose of 5-FU was further reduced to 1600 mg m⁻² for subsequent cycles if grade 4 thrombocytopenia or neutropenia developed again after first level of dose reduction of 5-FU. Oxaliplatin was decreased to 50 mg m⁻² if grade 4 thrombocytopenia or neutropenia developed after two levels of 5-FU dose reduction. If grade 3–4 nonhaematological toxicities or grade 2 hand–foot syndrome developed, 5-FU was decreased to 2000 mg m⁻² for subsequent cycles. Dose of 5-FU was further decreased to 1600 mg m⁻² for subsequent cycles if grade 3–4 nonhaematological toxicities or grade 2 hand–foot syndrome recurred after first levels of dose reduction of 5-FU. Oxaliplatin was decreased to 50 mg m⁻² if grade 3–4 nonhaematological toxicities or grade 2 hand–foot syndrome developed again after two levels of 5-FU dose reduction. For grade 2–3 neurotoxicities, oxaliplatin was omitted until recovery of the neurotoxicities to grade 1 or less; and the dose of oxaliplatin was decreased to 50 mg m⁻² for subsequent cycles. Oxaliplatin was discontinued if grade 2–3 neurotoxicities lasted for more than 3 weeks.

Evaluation of efficacy and toxicities

Evaluations before chemotherapy included medical history taking, physical examination, complete blood count, blood chemistry, chest X-ray, computed tomography (CT) scan of abdomen, and gastroendoscopy. After starting protocol treatment, complete blood count was examined weekly and blood chemistry every 3 weeks. Patients’ condition and treatment-related toxicities were evaluated weekly. Tumour size was measured by imaging studies every 6 weeks. Tumour response was evaluated according to the World Health Organization criteria. Toxicities were graded using the NCI-Common Toxicity Criteria (version 1).

Statistical methods

The Simon two-stage design was used. The response rates of interest were $P_b = 40\%$ and $P_t = 60\%$. If there were more than 12 responses in 29 patients in the first stage, the study would continue to 54 patients in the second stage. If there were more than 27 responses in 54 patients in the second stage, this treatment would be acceptable with $\alpha = 0.05$ and $\beta = 0.10$.

Time to progression was defined as the duration from the date of starting protocol treatment to the date of documented disease progression or death by any cause. The overall survival was defined as the duration from the date of starting protocol treatment to the date of death. Kaplan–Meier method was used in all survival analyses.

RESULTS

Patients and treatment

Between January 2001 through January 2002, 55 patients were enrolled into the study. Major clinicopathologic features of the patients are listed in Table 1. The median age of the patients was 64 years (range: 22–75). A total of 323 cycles (median: 6, range: 1–17) of chemotherapy were given. Median relative dose intensity was 95% (range: 67–100%) for oxaliplatin, 95% (range: 48–100%) for 5-FU, and 95% (range: 48–100%) for FA. Oxaliplatin has a cumulative toxicity, the median relative dose intensity of oxaliplatin was 100% (range: 70–100%) at cycle 3 and 88% (range: 67–100%) at cycle 6, respectively. In total, 75% of the patients received more than 80% of intended doses of oxaliplatin, 5-FU and FA.
Efficacy

Five patients were not evaluable for response: four failed to return to the clinic for tumour measurements and one later found to have nonmeasurable tumours. Of the 50 patients evaluable for tumour response, there were 28 patients with partial remission (PR), four patients with stable disease (SD), and 18 patients with progressive disease (PD). The total tumour response rate was 56% (95% CI: 41.8–70.3%). The median time to tumour response was 3 months (range: 2.2–8.3 months). Five out of the six patients, who had previously received postoperative adjuvant chemotherapy which contains cisplatin and 5-FU, achieved PR. Two responders went on to receive curative surgical resection or radiotherapy for the residual tumours. Both patients were alive and tumour-free at 16 and 25 months after starting protocol chemotherapy, respectively.

Median follow-up time of the whole group of 55 patients was 24.0 months as cut-off date for analysis on 25 July 2003. The median time to progression was 5.2 months (95% CI: 4.0–7.0 months) (Figure 1). The median overall survival was 10.0 months (95% CI: 8.0–13.3 months) (Figure 2).

Toxicity

All 55 patients were evaluated for toxicities (Table 2). Nine patients (14.5%) discontinued treatment because of treatment-related toxicity. Eight out of these nine patients discontinued treatment because of oxaliplatin-related neurotoxicity. The median dose of oxaliplatin received by these eight patients was 910 mg m$^{-2}$ (range: 715–1170 mg m$^{-2}$). Another patient discontinued treatment due to heart failure, which was considered unrelated to chemotherapy.

### Table 1  Clinicopathologic features of the patients

| Patient number (%) |
|-------------------|
| Total patients    | 55 |
| Sex: male/female  | 36/19 |
| ECOG performance  | |
| 0                 | 9 (16.4) |
| 1                 | 39 (70.9) |
| 2                 | 7 (12.7) |
| Treatments for primary tumour | |
| No prior therapy  | 31 (56.4) |
| Surgery only      | 18 (32.7) |
| Surgery + adjuvant chemotherapy | 6 (10.9) |
| Disease status    | |
| Locally advanced  | 3 (5.5) |
| Recurrence/metastasis | 52 (94.6%) |
| Disease sites     | |
| Liver             | 26 (47.3) |
| Lymph nodes       | 28 (50.9) |
| Peritoneum        | 15 (27.3) |
| Gastrointestinal tract | 9 (16.4) |
| Bone              | 9 (16.4) |
| Lung              | 5 (9.1) |
| Others            | 11 (20) |

### Table 2  Toxicity of the oxaliplatin-HDFL regimen

| Toxicity                  | Grade 1–2 | Grade 3–4 | Grade 1–2 | Grade 3–4 |
|---------------------------|-----------|-----------|-----------|-----------|
| Haematological            |           |           |           |           |
| Neutropenia               | 72.7$^a$  | 21.8      | 34.3$^b$  | 7.1       |
| Leukopenia                | 58.1      | 7.2       | 21.0      | 1.8       |
| Thrombocytopenia          | 60.0      | 12.7      | 24.5      | 5.0       |
| Febrile neutropenia       | 1.8       | 5.4       | 0.3       | 0.9       |
| Anaemia                   | 61.8      | 9.0       | 34.7      | 2.8       |
| Gastrointestinal          |           |           |           |           |
| Nausea                    | 81.8      | 10.9      | 38.4      | 2.5       |
| Vomiting                  | 87.2      | 12.7      | 31.6      | 2.2       |
| Diarrhoea                 | 69.1      | 12.7      | 22.0      | 2.4       |
| Stomatitis                | 50.9      | 3.6       | 13.3      | 0.9       |
| Anorexia                  | 70.9      | 1.8       | 36.5      | 0.3       |
| Weight loss               | 9.1       | 0         | 1.85      | 0         |
| Neuropathic               | 72.7      | 12.7      | 46.8      | 2.2       |
| Others                    |           |           |           |           |
| Cardiac                   | 0         | 1.8       | 0         | 0.3       |
| Fever                     | 27.3      | 1.8       | 7.1       | 0.3       |
| Infection without neutropenia | 16.4 | 0       | 4.3       | 0         |
| Alopecia                  | 21.8      | 0         | 16.4      | 0         |

$^a$All numbers are percentage of the 55 patients. $^b$All numbers are percentage of the 323 cycles given.
DISCUSSION

The results of this phase II study indicated that weekly oxaliplatin and 24-h infusion of high-dose 5-FU and FA is an effective combination chemotherapy for advanced gastric cancer. The overall response rate of 36% was within the range (30–70%) of previous major protocols such as FAMTX, ELF, EAP, ECF, and recent taxane-based (Bokemeyer et al, 1997; Kollmannsberger et al, 2000; Cascini et al, 2001) or irinotecan-based regimens (Blbeberg, 1999; Ajani et al, 2002; Slater et al, 2002). Recently, three other studies, using different administering schedules of oxaliplatin and 5-FU, have also demonstrated a good efficacy in gastric cancer (Louvet et al, 2002; Kim et al, 2003; Al-Batran et al, 2004). These phase II studies showed a response rates of 43–44.9% (Louvet et al, 2002; Al-Batran et al, 2004) and 26% (Kim et al, 2003) in the first- and second-line treatment, respectively. Oxaliplatin appears to be a useful adjunct to systemic chemotherapy against advanced gastric cancer. Currently, a randomised multicentre study (REAL-2) is underway with a two by two factorial design to compare the efficacy of capecitabine with 5-FU, and oxaliplatin with cisplatin in the ECF regimen, for patients with advanced oesophagogastric cancer. The study aims to enroll 1000 patients with the primary end point being 1-year survival. The interim analysis of the REAL-2 study showed good antitumour activity in favour of oxaliplatin and capecitabine with a response rate of 52% (95% CI: 34.4–68.1%) in an EOX (epirubicin, oxaliplatin, capecitabine) regimen (Sumpter et al, 2003).

In this study, 5-FU and FA was given by two weekly 24-h infusion (the HDFL regimen) every 3 weeks. The rationale of this scheduling for 5-FU was based on our previous observations which indicated that HDFL is in general a highly effective and very safe regimen for advanced gastric cancer (Hsu et al, 1997; Yeh and Cheng, 1998). The patients' compliance was excellent. To avoid calcite precipitation and catheter blockage (Ardalan 1991, 1995), we decreased the dose of FA from 500 to 300 mg m\(^{-2}\), respectively. Oxaliplatin appears to be a useful adjunct to systemic chemotherapy against advanced gastric cancer. Currently, a randomised multicentre study (REAL-2) is underway with a two by two factorial design to compare the efficacy of capecitabine with 5-FU, and oxaliplatin with cisplatin in the ECF regimen, for patients with advanced oesophagogastric cancer. The study aims to enroll 1000 patients with the primary end point being 1-year survival. The interim analysis of the REAL-2 study showed good antitumour activity in favour of oxaliplatin and capecitabine with a response rate of 52% (95% CI: 34.4–68.1%) in an EOX (epirubicin, oxaliplatin, capecitabine) regimen (Sumpter et al, 2003).

It is noteworthy that the response rate of 36% comparing well to the ECF regimen (26% in phase II studies). The HDFL regimen may be an alternative regimen for patients with advanced gastric cancer. However, the haematological toxicity of the present study is still favourable and well tolerated. Neurotoxicity was also found to be the predominant dose-limiting toxicity in another oxaliplatin-containing regimen for gastric cancer (Louvet et al, 2002). Other major toxicities, including neutropenia, thrombocytopenia, stomatitis, and diarrhoea, were of the same range of severity as other major regimens such as FAMTX, ECF, FUP, ELF, and FOLFFOX (Webb et al, 1997; Vanhoef er et al, 2000; Louvet et al, 2002). Owing to patients’ selection in phase II studies, it may not be possible or relevant to compare the toxicity profiles of the present study with three other phase II studies, using different administering schedules of oxaliplatin and 5-FU in gastric cancer (Louvet et al, 2002; Kim et al, 2003; Al-Batran et al, 2004). However, the haematological toxicity of the present study is still favourable and well tolerated with grade 3–4 neutropenia and febrile neutropenia of 7.1 and 0.9%, respectively, in a total of 325 cycles given. Further, the absence of grade-2 alopecia in this study compared favourably to other regimens.

We conclude that combination of weekly oxaliplatin and weekly 24-h infusion of 5-FU and FA is an active regimen with acceptable toxicities for the treatment of advanced gastric cancer.

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