## Original Article

# A pilot study evaluating the safety and toxicity of epirubicin, cisplatin, and UFT (ECU regimen) in advanced gastric carcinoma

Sezer Saglam[1], N Faruk Aykan[1], Burak Sakar[1], Mine Gulluoglu[2], Emre Balik[3], Hasan Karanlik[4]

*[1]Departments of Medical Oncology, Istanbul University Oncology Institue; [2]Pathology, Istanbul Medical Faculty, Istanbul University; [3]Department of General Surgery, Istanbul Medical Faculty, Istanbul University, [4]Department of General Surgery, Istanbul University Oncology Institue, Istanbul, Turkey*

**ABSTRACT**

**Background:** Best response rates have been achieved with three-drug regimens containing 5-FU in the treatment of advanced gastric cancer (AGC) and oral fluoropyrimidines are the best alternatives as substitutes for infusional 5-FU. This study aimed to evaluate the safety and toxicity of epirubicin, cisplatin, and UFT (ECU regimen) regimens in AGC outpatients.

**Materials and methods:** Forty-one patients with AGC received epirubicin, cisplatin, and oral UFT plus leucovorin. Epirubicin 50 mg/m$^2$ and cisplatin 60mg/m$^2$ were administered on Day 1. Three hundreds (300) mg/m$^2$/day UFT was administered with leucovorin at a fixed oral dose of 90 mg/day for 21 days, followed by a 7-day rest period. Cycles were repeated every 4 weeks. Performance status was either as 0 and 1.

**Results:** Among the 41 patients enrolled, complete and partial response was achieved in 7.3% and 36.6% of patients, respectively, with an overall response rate of 43.9%. Stable disease was observed in 34.1% of patients and 22% showed disease progression. Median time to progression was 5.2 months and median survival was 12.3 months. A median of 4 cycles (range: 1-6) of chemotherapy were administered. The main grade III-IV toxicities were nausea/vomiting (19.4%) and neutropenia (12.1%). Grade IV toxicities were gastric perforation and renal failure.

**Conclusion:** ECU appears to be an effective regimen in the treatment of AGC, with acceptable tolerability and manageable toxicity. In three-drug regimens, substitution of infusional 5-FU by UFT offers the possibility of increased AGC outpatient compliance.

**KEY WORDS** advanced gastric carcinoma, cisplatin, epirubicin, UFT

J Gastrointest Oncol 2011; 2: 19-26. DOI: 10.3978/j.issn.2078-6891.2010.030

## Introduction

Gastric cancer is one of the most challenging diseases among all cancer types. It is the fourth most common cancer worldwide, with an estimated 934 000 new cases per year in 2002 (9% of new cases globally), and occurs nearly twice as often in men (1). In the United States, mortality due to gastric cancer has declined and five-year relative survival rates improved from 16% to 24% between 1975 and 2002 (2). In Turkey, gastric cancer is the second leading cause of death in men and the third leading cause of cancer mortality in women (3). The anatomical site of origin of gastric cancer among Turkish patients differs from that reported for Western countries, with 48.1% and 41.2% of cancers in Turkish patients occurring at the antrum and corpus, respectively, and 51.6% of patients having a pathological grade III cancer (4).

Surgery is the main treatment modality for gastric cancer. Only in Japan, the majority of patients are surgically treated at stage I (5). The reported median survival benefit in AGC patients receiving chemotherapy is approximately 6 months

No potential conflict of interest.

Corresponding to: Sezer Saglam, MD. Istanbul University Oncology Institute, Department of Medical Oncology, Capa 34093, Istanbul, Turkey. Tel: +90-542-2369776; Fax: +90-212-5348078. Email: saglam@istanbul.edu.tr.

Submitted Oct 05, 2010. Accepted for publication Dec 29, 2010.
Available at www.thejgo.org

ISSN: 2078-6891

(6), and the reported benefits of novel chemotherapy regimens for AGC have been shown to not exceed 12 months in recent Phase III trials in Western countries (7,8).

Fluorouracil- (5-FU) based chemotherapies are the mainstay of treatment for AGC. Since continuous 5-FU infusion has shown promising results in the treatment of AGC in Phase II trials, combination therapies have been developed (9). Oral fluoropyrimidines are the best alternative to infusional 5-FU in three-drug regimens for AGC. Tegafur (UFT) is an oral fluoropyrimidine and its antitumor activity is known to generate plasma 5-FU levels that are similar to those of infusional 5-FU (10-12).

This pilot study was conducted to examine the safety and toxicity of combination chemotherapy consisting of epirubicin, cisplatin, and UFT regimen in chemo-naïve AGC outpatients.

## Patients and methods

### *Patients*

Forty-one AGC patients who admitted to Istanbul University Oncology Institute between September 2003 and December 2006 were included in this study. Patients with histologically or surgically proven metastatic or locally advanced inoperable gastric carcinoma were eligible. They were required to have a performance status (PS) level of (0) or (1) according to WHO criteria. There was no age limit. Informed consent was obtained from all patients and the study was approved by the Institutional Review Board. All patients were required to have a leukocyte count ≥ 4000/μL; platelet count ≥ 100 000/μL; hemoglobin ≥ 10.0 g/dL; aspartate transaminase (AST) and aminotransferase (ALT) below two times the upper normal limit; creatinine serum level ≤ 1.3 mg/dL; and total serum bilirubin < 2 mg/dL. Exclusion criteria included patients who had received any type of previous adjuvant treatment and patients with other types of tumors, heart or lung failure, myocardial infarction, previous chemotherapy, brain metastasis, active infection, breast-feeding, or pregnancy.

### *Drug administration and dose adjustments*

The following regimen was given to patients: cisplatin (60 mg/m$^2$) IV 1-hour infusion with standard hydration on Day 1; epirubicin (50mg/m$^2$) IV 30 minutes infusion on day 1; UFT (Tegafur/uracil; Bristol Myers Squibb, Spain) 300 mg/m$^2$ taken orally on days 1-21 (q 28-d); and leucovorin (Rescuvolin®, Netherlands) administered 90 mg/day orally on days 1-21 (q 28-d).

The total daily dose of UFT was divided into three doses given every 8 hours, beginning with an initial dose of 300 mg/m$^2$/day. UFT was supplied in the form of 100 mg capsules (100 mg tegafur and 225 mg uracil). Leucovorin was supplied as 15 mg oral tablets and the fixed total daily dose (90 mg) was divided into three doses. Treatment was repeated every 4 weeks until disease progression, patient refusal, intolerance to therapy, or unacceptable adverse reactions occurred.

ECU regimen dose reduction was planned in the event of severe hematological and/or non-hematological toxic events. Hematological tests were performed at baseline in all patients and they were repeated in asymptomatic patients before the beginning of each cycle. In patients with signs and symptoms of hematological toxicity, the tests were ordered at the onset of the symptoms and weekly thereafter until the condition resolved. The doses of UFT, epirubicin, and cisplatin were reduced 25% in subsequent cycles in the event of the following conditions: 1) Grade III-IV neutropenia or thrombocytopenia lasting for seven days or more, and 2) Grade IV non-hematological toxicity. In cases of insufficient hematological function (neutrophil count <1500/μL and platelet count <100 000/μL) chemotherapy was delayed for as long as 14 days. If no recovery occurred at this point, treatment was discontinued. A maximum of 2 dose reductions were allowed per patient. Cisplatin doses were reduced 25% when the creatinine level was between 1.4 and 1.9 mg/dl. For a creatinine level between 2.0 and 2.2 mg/dl, a 50% dose reduction was allowed.

### *Study end points and evaluation of treatment*

This was a single-center pilot study. The primary objective was to evaluate the safety and toxicity of the ECU regimen in AGC outpatients. The secondary objectives were to determine time to progression (TTP), overall survival (OS) rates, and response rates. Toxicity was graded and defined using NCI CTC Version 2. RECIST criteria were used to assess response to treatment. For the evaluation of response, the extent of measurable disease was assessed by computerized tomography before the first cycle and after every 2 cycles. Time to progression was defined as the duration from the initiation of the regimen to the date of documented disease progression or death by any cause. Overall survival was defined as the duration from initiation of chemotherapy to the date of death or last follow-up.

### *Statistical analysis*

Kaplan-Meier analysis was used for TTP and overall survival analyses and the log-rank test was used for comparisons. Survivors were censored on the date they were last known to be alive.

## Results

### *Patient characteristics*

Patient characteristics are shown in Table 1. No patient was withdrawn from the study. All patients had PS 0 or PS1. Two patients (4.9%) had gastroesophageal adenocarcinomas, 15 (36.6 %) had corpus tumors, and 17 (41.5%) had antral tumors. Twenty-two patients (53.7%) had histopathologically grade III tumors and 19 (46.3%) had grade II tumors. Eight patients (19.5%) had locally advanced tumors and the remaining had metastatic disease. Median age of patients was 54 (range: 26-71).

### *Response to chemotherapy*

One-hundred fifty-nine courses of treatment were administered. The median delivered dose intensities of epirubicin, cisplatin, and oral UFT were 91.8%, 92.5%, and 91.2%, respectively. The median number of chemotherapy cycles was 4 (range: 1-6) and average duration of follow-up was 12.7 months (range: 2.9-49.5) (Table 2).

Three patients (7.3%) had complete response after 6 (n=2) or 4 cycles (n=1). Fifteen patients (36.6%) had partial response and 14 (34.1%) had stable disease. Nine patients (22%) showed progression. The overall response rate was 43.9% (complete response plus partial response) (95% CI; 28.5-60.3) (Table 2).

Twelve patients (29.2%) required dose modification only once during treatment and 2 patients (4.9%) required dose modification twice. Of the 2 patients with locally advanced disease who underwent surgery after 6 cycles of chemotherapy, 1 is still alive and the other died due to postoperative complications. Brain metastasis developed in one patient after 3 cycles of chemotherapy.

### *Toxicity*

The main grade III-IV non-hematological toxicities encountered with the ECU regimen were nausea and vomiting (19.5%). Neutropenia was the main grade III-IV hematological toxicity (12.1%; Table 3). Grade III-IV diarrhea occurred in 4 patients (9.8%). Reasons for dose modifications were prolonged neutropenia, neutropenic fever, hypopotassemia, diarrhea, and anorexia.

The most serious grade IV adverse events included acute renal failure (2.4%) and gastric perforation (2.4%). A gastric perforation that occurred after 1 cycle of chemotherapy in a patient with locally advanced disease was repaired surgically and the patient continued treatment with 4 cycles of cisplatin and infusional 5-FU and survived for 23 months.

Acute renal failure developed in 1 female patient due to grade IV diarrhea, nausea, and vomiting after the fifth cycle. She did not seek medical help immediately, resulting in a

**Table 1 Patient characteristics (n=41)**

| Characteristic | |
|---|---|
| Median age, y (range) | 41 (26-71) |
| Male/female ratio | 31/10 |
| WHO performance status | |
| 0 | 19 (46.3%) |
| 1 | 22 (53.7%) |
| No prior treatment | 41 (100%) |
| Surgically diagnosed | 7 (17.0%) |
| Primary metastatic | 26 (63.4%) |
| Locally advanced | 8 (19.5%) |
| Disease location | |
| Gastroesophageal | 2 (4.9%) |
| Linitis plastica | 7 (17.0%) |
| Corpus | 15 (36.6%) |
| Antrum | 17 (41.5%) |
| Site of measurable disease* | |
| Liver | 15 (36.6%) |
| Liver and peritoneal | 3 (7.3%) |
| Krukenberg tumor | 2 (4.9%) |
| Locally advanced | 8 (19.5%) |
| Abdominal lymph node | 4 (9.7%) |
| Site of non-measurable disease | |
| Peritoneal disease | 9 (22.0%) |
| Tumor grade | |
| Grade II | 19 (46.3%) |
| Grade III | 22 (53.7%) |

Unless otherwise stated, data are presented as n (%). *A measurable disease had to be dimensionally measurable.

**Table 2 Treatment response**

| Definition of response | n=41 |
|---|---|
| Complete response | 3 (7.3%) |
| Partial response | 15 (36.6%) |
| Stable disease | 14 (34.1%) |
| Progressive disease | 9 (22.0%) |
| Overall response | 18 (43.9%) |
| Median time to progression (months) | 5.2 |
| Median survival (months) | 12.3 |

Unless otherwise stated, data are presented as n (%).

**Table 3 Grade I-II to IV toxicity during ECU treatment (n=41)**

| | Grade | | |
|---|---|---|---|
| | I-II n (%) | III n (%) | IV n (%) |
| Non-hematological toxicity | | | |
| Nausea and vomiting | 7 (17.0%) | 7 (17.0%) | 1 (2.4%) |
| Stomatitis/mucositis | 4 (9.7%) | - | - |
| Diarrhea | 6 (14.6%) | 2 (4.9%) | 2 (4.9%) |
| Anorexia | 7 (17.0%) | 1 (2.4%) | - |
| Fatigue | 5 (12.1%) | - | - |
| Acute renal failure | - | - | 1 (2.4%) |
| Thrombosis | - | 2 (4.9%) | - |
| Hypopotassemia | - | 1 (2.4%) | - |
| Gastric perforation | - | - | 1 (2.4%) |
| Hematological toxicity | | | |
| Neutropenia | 6 (14.6%) | 4 (9.5%) | 1 (2.4%) |
| Decreased hemoglobin levels | 8 (19.4%) | 2 (4.9%) | - |
| Leukopenia | 7 (17.0%) | 2 (4.9%) | 1 (2.4%) |

delayed admission to hospital. She was subsequently treated with hemodialysis and recovered.

Grade III hypokalemia occurred in 1 patient (2.4%) without diarrhea, nausea, or vomiting. Deep vein and portal vein thrombosis developed in 2 other patients (4.9%) who were considered to have disease progression. There were no chemotherapy-related deaths. Eight patients (19.5%) discontinued chemotherapy due to intolerance after 1 to 5 cycles. Toxicity-related treatment delays were observed in 17 patients (41.5%).

***Survival***

Median time to progression was 5.2 months (95% CI: 0.53 -9.86) and median overall survival was 12.3 months (95% CI: 5.3-19.3) (Fig 1). One year survival was 68.4% for patients with grade II tumors (16.3 months; 95%CI: 10.6-21.9) and 27.3% for those with grade III tumors (7.3 months; 95% CI: 5.62-8.41), corresponding to a significant difference in survival rate ($P$=0.05) (Fig 2).

## Discussion

Management of AGC has been evolving since the 1990' s. Pyrhonen showed the advantage of chemotherapy compared to best supportive care (BSC) in AGC in a small sample size using bolus 5-FU (13). Findlay showed that the administration of epirubicin, cisplatin, and continuous infusion 5-FU (ECF) was associated with an objective tumor response rate of 71% (14). These encouraging results led to a randomized trial in which ECF was compared with FAMTX (fluorouracil-doxorubicin-methotrexate) (15). In that study, median survival of patients receiving ECF (8.9 months) was also better, compared to FAMTX (5.7 months). As a result, the benefits of infusional 5-FU in the treatment of AGC was definitively established for the first time in terms of clinical response and overall survival. Folates are known to prolong the retention of the 5-fluoro-2'-deoxyuridine 5'-monophosphate (FdUMP)-TS complex (16). Inhibition of TS by FdUMP is thought to be the primary mechanism for the action of 5-FU (17). A two-drug regimen consisting of cisplatin and 5-FU was shown to decrease TS mRNA levels in adenocarcinoma of the stomach, which explains the mechanism of action of combination therapies (18). Subsequent meta-analyses showed best results with three-drug regimens in AGC patients (6).

UFT is a combination (in a 1:4 M ratio) of tegafur, an oral prodrug of 5-FU that is metabolized to 5-FU primarily in the liver, and uracil, a natural substrate for the liver enzyme dihydropyrimidine dehydrogenase (DPD). Compound uracil serves as a competitive antagonist for DPD and enhances the concentration and half-life of 5-FU (11,12). UFT is administered alone or with folinic acid (leucovorin) tablets to increase the effect on thymidylate synthetase (TS).

Oral UFT monotherapy with leucovorin has shown overall response rates (ORRs) of 10.5-28% and median OS rates of 5.8-6.1 months (19,20), which is similar to

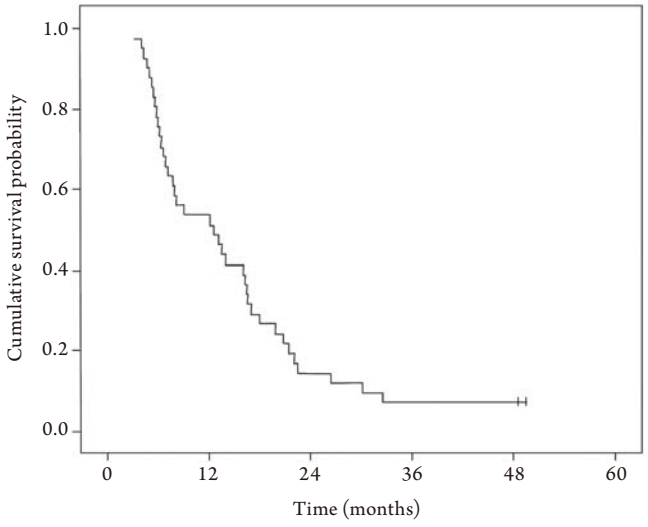


**Figure 1 Kaplan-Meier curve for the cumulative survival probability of all patients**

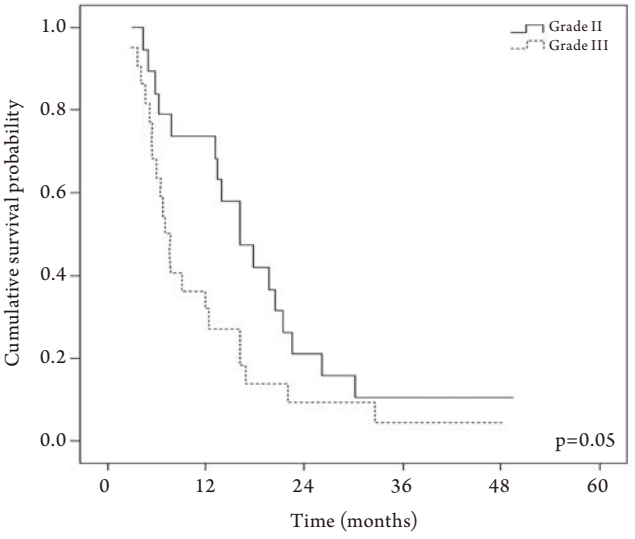


**Figure 2 Kaplan-Meier curves showing the significant survival difference between grade II and grade III tumors**

those reported for 5-FU single-agent continuous infusion (11). ORRs with two-drug regimens (UFT and cisplatin, etoposide, or paclitaxel) were 35%-51% and average OS was 8.1-10.1 months in the treatment of AGC patients (21-23). Finally, three-drug regimens with oral UFT have shown promising results in the treatment of AGC (24-28). Even complete remission of AGC has been reported using the suppository form of UFT (29). UFT is absorbed readily in the gastrointestinal system, which helps improve patient compliance and maintain constant plasma levels of 5-FU. In addition, catheter-related complications are avoided (30).

Although UFT and leucovorin doses have been studied for the last two decades, to date, an optimal administration schedule has not been established. The goal of adding leucovorin is to increase efficacy without additional toxicity. Newman (31) and Buroker et al. (32) showed no survival advantage of high-dose leucovorin but observed increased toxicity. On the other hand, in a randomized study of colon cancer patients, Köhne et al. found a benefit only in terms of better progression-free survival when leucovorin was added to 5-FU (33). However, this benefit was at the expense of increased toxicity. Pazdur et al. showed that UFT with leucovorin was equal to FUFA in colon cancer treatment, with less toxicity in favor of UFT (34). No studies have ever compared UFT versus UFT/LV treatment in gastric and colon cancers, but colon cancer studies usually provide guidance for approximate UFT doses. Fixed leucovorin doses between 25 mg/m$^2$ and 90 mg/m$^2$ have been given to patients, but it is primarily the UFT dose that accounts for the overall response rate and toxicity (22,27-30). Therefore, low doses of leucovorin might be recommended as opposed to not implementing UFT at all.

In this study, administration of the ECU regimen in AGC patients was associated with acceptable toxicity. The most serious toxicities observed were gastric perforation and acute renal failure. The patient with gastric perforation had locally advanced linitis plastica and lived for 23 months. This is a very rare complication, with only one case reported in the after a single cycle of UFT (35). Perforation may be attributed to impaired connective tissue repair induced by chemotherapy in the tumors (36) and/or it may be the result of chemosensivity. The other serious toxicity event was acute renal failure, which was directly related to delayed hospitalization for grade IV diarrhea, vomiting, and nausea. Previously, Woo reported a patient with grade IV diarrhea, vomiting, and nausea who required a 75% reduction in cisplatin dose (29), and Kim reported one case with grade IV diarrhea that received the same three-drug UFT regimen and required hospitalization (27).

In this study, grade III-IV mucositis was not observed, but grade III-IV diarrhea occurred in 4 patients (9.8%). If UFT doses as high as 480 mg/m$^2$ had been used as a single agent, more cases with grade III-IV mucositis and diarrhea might have been observed (29). In a study by Kim et al., grade III-IV mucositis was reported in 13% of patients receiving a UFT dose of 360 mg/m$^2$, while other studies reported mucositis in 6% of subjects receiving 300 mg/m$^2$ UFT in ECU regimens. The incidence of diarrhea was also higher in the former study (10.8% *vs* <6%) (24-27).

The incidence of grade III-IV neutropenia (11.9%)

**Table 4 Previous studies with epirubicin, cisplatin, UFT regimens**

| Study | UFT regimen | N | PS | PS 2 (%) | MC | OR | OS |
|---|---|---|---|---|---|---|---|
| Kim et al.,1999 (24) | UFT: 360 mg/m$^2$<br>LV: 25 mg/day<br>D1-21/q28 | 37 | 0,1,3 | PS 3 (18.9%) | (4) | 54% | 10.0 |
| Jeen et al., 2001 (25) | UFT: 300 mg/m$^2$<br>LV: 30 mg/day<br>D1-21/q28 | 47 | 0-2 | 25% | (5) | 57.5% | 15.0 |
| Woo et al., 2005 (26) | UFT: 300 mg/m$^2$<br>LV: 45 mg/m$^2$/day<br>D1-21/q21 | 35 | 0-2 | 34% | (4) | 40.6% | 7.1 |
| Idelevic et al., 2007 (27) | UFT: 300 mg/m$^2$<br>LV: 30 mg/m$^2$/day<br>D1-22/q28 | 39 | 0-2 | 21% | (5) | 38% | 9.5 |
| Saglam et al., 2010<br>(Present study) | UFT: 300 mg/m$^2$<br>LV: 90 mg/m$^2$/day<br>D1-22/q28 | 41 | 0-1 | - | (4) | 43.9% | 12.3 |

Abbreviations: N, number of patients; PS, performance status; MC, median cycle of chemotherapy; OR, overall response; OS, overall survival in months; D, day; LV, leucovorin.

was lower in this study compared to other studies with epirubicin, cisplatin, and UFT regimens (24-27,29). A 1-week drug-free interval after 3 weeks of UFT administration, the exclusion of patients with PS 2, and no UFT doses above 300 mg/m$^2$ may account for this low incidence (Table 4). Hand-foot syndrome, neurotoxicity, or cardiac problems were not observed in this study, which may be attributed to the uracil component of UFT, since it is known to prevent skin exfoliation and cardiac events (37-40). Thrombosis occurred in 2 patients (4.9%). Thrombosis is an important toxicity event during the treatment of AGC; it occurs frequently at the initiation and during the course of chemotherapy, resulting in poor OS (41).

In addition to its acceptable toxicity profile and convenience of administration on an outpatient basis, the ECU regimen also appears to be promising in terms of efficacy. Overall median survival was 12.3 months compared to 8.2 months obtained in a previous study with the ECF regimen (epirubicin, cisplatin, infusional 5-fluorouracil) (14). Conversely, overall response rates varied between 25% and 71% in studies using the ECF regimen for AGC (14,42), whereas they varied between 38% and 54% in studies with the ECU regimen (including this study) (24,25). Therefore, the efficacy of ECU versus ECF needs to be studied in larger controlled trials.

One-year survival rates for Grade II and Grade III tumors were 68.4% and 27.3%, respectively ($P$=0.05). The proportion of patients with grade III tumors in this study is close to the general profile of Turkish patients with AGC (4). In future studies, the efficacy and safety of the ECU regimen should be studied in patients with different pathological grades. Another important factor affecting treatment outcome is the performance status of patients with AGC. It has a direct impact on survival, as shown in a meta-analysis by Yoshida in AGC (43) . The relationship between performance status and survival can be seen in Table 4.

## Conclusion

This study has shown the feasibility of the ECU chemotherapy regimen, with manageable toxicity in an outpatient setting for patients with AGC. UFT could be considered as a substitute for infusional 5-FU and the ECU regimen might represent a treatment model for three-drug regimens for the management of AGC.

## References

1 Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. CA Cancer J Clin 2005;55:74-108.

2 Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57:43-66.

3 Sengelen M, Kutluk T, Fırat D. Cancer Statistics in Turkey and in the World 1996-2003. 1st edition Turkish Association for Cancer Research and Control, 2007. p46

4 Demir G, Zengin N, Yıldız O. Clinical profile of gastric cancer in Turkey: Factors effecting disease free survival and relapse (Turkish Oncology Group Study). Annals of Oncology 2006;17:Abtract :1139 and updated, unpublished data with personal communication

5 Maruyama K, Kaminishi M, Hayashi K, Isobe Y, Honda I, Katai H, et al. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer 2006;9:51-66.

6 Wagner AD, Grothe W, Haerting J, Kleber G, Grothey A, Fleig WE. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol 2006;24:2903-9.

7 Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol 2006;24:4991-7.

8 Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med 2008;358:36-46.

9 Moynihan T, Hansen R, Anderson T, Quebbeman E, Beatty P, Ausman R, et al. Continuous 5-fluorouracil infusion in advanced gastric carcinoma. Am J Clin Oncol 1988;11:461-4.

10 Fujii S, Nakamura Y, Takeda S, Morita K, Sato T, Marunaka T, et al. Metabolism, antitumor activity, and acute toxicity of 5-fluoro-1,3-bis(tetrahydro-2-furanyl)-2,4-pyrimidinedione by oral administration to animals. Gann 1980;71:30-44.

11 Meropol NJ, Rustum YM, Petrelli NJ, Rodriguez-Bigas M, Frank C, Ho DH, et al. A phase I and pharmacokinetic study of oral uracil, ftorafur, and leucovorin in patients with advanced cancer. Cancer Chemother Pharmacol 1996;37:581-6.

12 Ho DH, Pazdur R, Covington W, Brown N, Huo YY, Lassere Y, et al. Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N1-(2'-tetrahydrofuryl)-5-fluorouracil. Clin Cancer Res 1998;4:2085-8.

13 Pyrhonen S, Kuitunen T, Nyandoto P, Kouri M. Randomised comparison of fluorouracil, epidoxorubicin and methotrexate (FEMTX) plus supportive care with supportive care alone in patients with non-resectable gastric cancer. Br J Cancer 1995;71:587-91.

14 Findlay M, Cunningham D, Norman A, Mansi J, Nicolson M, Hickish T, et al. A phase II study in advanced gastro-esophageal cancer using epirubicin and cisplatin in combination with continuous infusion 5-fluorouracil (ECF). Ann Oncol 1994;5:609-16.

15 Webb A, Cunningham D, Scarffe JH, Harper P, Norman A, Joffe JK, et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil versus fluorouracil, doxorubicin, and methotrexate in advanced esophagogastric cancer. J Clin Oncol 1997;15:261-7.

16 Okabe H, Toko T, Saito H, Nakano K, Fujioka A, Yuasa C, et al. Augmentation of the chemotherapeutic effectiveness of UFT, a combination of tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] with uracil, by oral l-leucovorin. Anticancer Res 1997;17:157-64.

17 Copur S, Aiba K, Drake JC, Allegra CJ, Chu E. Thymidylate synthase gene amplification in human colon cancer cell lines resistant to 5-fluorouracil. Biochem Pharmacol 1995;49:1419-26.

18 Lenz HJ, Leichman CG, Danenberg KD, Danenberg PV, Groshen S, Cohen H, et al. Thymidylate synthase mRNA level in adenocarcinoma of the stomach: a predictor for primary tumor response and overall survival. J Clin Oncol 1996;14:176-82.

19 Kim YH, Cheong SK, Lee JD, Park JS, Shin SW, Kim JS. Phase II trial of Oral UFT and leucovorin in advanced gastric carcinoma. Am J Clin Oncol 1996;19:212-6.

20 Ravaud A, Borner M, Schellens JH, Geoffrois L, Schoffski BP, Kroon K, et al. UFT and leucovorin in first-line chemotherapy for patients with metastatic gastric cancer. An Early Clinical Studies Group (ECSG)/European Organization for Research Treatment of Cancer (EORTC) phase II trial. Eur J Cancer 2001;37:1642-7.

21 Suga S, Iwase H, Shimada M, Nishio Y, Ichihara T, Ichihara S, et al. Neoadjuvant chemotherapy in scirrhous cancer of the stomach using uracil and tegafur and cisplatin. Intern Med 1996;35:930-6.

22 Sato A, Kurihara M, Koizumi W. A phase II study of UFT plus cisplatin (UFTP) therapy in patients with advanced gastric cancer. Proc Am Soc Clin Oncol 2000;19:Abstr 1087

23 Feliu J, Gonzalez Baron M, Garcia-Giron C, Espinosa E, Garcia-Alfonso P, Belon J, et al. Treatment of patients with advanced gastric carcinoma with the combination of etoposide plus oral tegafur modulated by uracil and leucovorin. A phase II study of the ONCOPAZ Cooperative Group. Cancer 1996;78:211-6.

24 Kim YH, Kim BS, Seo JH, Choi CW, Kim JS, Chun HJ, et al. Epirubicin, cisplatin, oral UFT, and calcium folinate in advanced gastric carcinoma. Oncology (Williston Park) 1999;13:64-8.

25 Jeen YT, Yoon SY, Shin SW, Kim BS, Mok YJ, Kim CS, et al. Phase II trial of epirubicin, cisplatin, oral uracil and tegafur, and leucovorin in patients with advanced gastric carcinoma. Cancer 2001;91:2288-93.

26 Woo IS, Moon DH, Shim BY, Lee MA, Byun JH, Kim KW, et al. A phase II study of epirubicin, cisplatin and uracil-tegafur for advanced gastric carcinoma. Jpn J Clin Oncol 2005;35:13-7.

27 Idelevich E, Karminsky N, Dinerman M, Katsenelson RL, Zvi NB, Baruch NB, et al. Phase II study of cisplatin, epirubicin, UFT, and leucovorin (PELUF) as first-line chemotherapy in metastatic gastric cancer. Acta Oncol 2007;46:324-9.

28 Aykan NF, Idelevich E. The role of UFT in advanced gastric cancer. Ann Oncol 2008;19:1045-52.

29 Hirose S, Hirahara K, Aoki S, Nakagawa H, Nishimura K, Hori M, et al. A case of complete regression of gastric carcinoma and liver metastases by treatment with tegafur. Gan To Kagaku Ryoho 1985;12:957-9.

30 Vescia S, Baumgartner AK, Jacobs VR, Kiechle-Bahat M, Rody A, Loibl S, et al. Management of venous port systems in oncology: a review of current evidence. Ann Oncol 2008;19:9-15.

31 Newman EM, Akman SA, Harrison JS, Leong LA, Margolin KA,

Morgan RJ, et al. Pharmacokinetics and toxicity of continuous infusion (6S)-folinic acid and bolus 5-fluorouracil in patients with advanced cancer. Cancer Res 1992;52:2408-12.

32 Buroker TR, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Mailliard JA, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. J Clin Oncol 1994;12:14-20.

33 Kohne CH, Wils J, Lorenz M, Schoffski P, Voigtmann R, Bokemeyer C, et al. Randomized phase III study of high-dose fluorouracil given as a weekly 24-hour infusion with or without leucovorin versus bolus fluorouracil plus leucovorin in advanced colorectal cancer: European organization of Research and Treatment of Cancer Gastrointestinal Group Study 40952. J Clin Oncol 2003;21:3721-8.

34 Pazdur R, Doulliard JY, Skillings J. Multicenter phase III study of 5-fluorouracil (5-FU) or UFT in combination with leucovorin (LV) in patients with metastatic colorectal cancer (Meeting abstract). Proc Am Soc Clin Oncol 1999:Abst 1009.

35 Imai H, Obana N, Iwabuchi T, Satou Y, Ooyauchi M, Igarashi T, et al. Long survival of advanced gastric cancer patient after total gastrectomy and postoperative treatment with S-1 despite S-1+CDDP+CPT-11 causing perforation. Gan To Kagaku Ryoho 2008;35:1185-8.

36 Bozdag AD, Peker Y, Derici H, Gurkok C, Ozgonul M. The effect of preoperative 5-fluorouracil on colonic healing: an experimental study. Hepatogastroenterology 2001;48:1631-4.

37 Yamamoto J, Haruno A, Yoshimura Y, Unemi N, Kunimune Y, Yamashita K, et al. Effect of coadministration of uracil on the toxicity of tegafur. J Pharm Sci 1984;73:212-4.

38 Houghton JA, Houghton PJ, Wooten RS. Mechanism of induction of gastrointestinal toxicity in the mouse by 5-fluorouracil, 5-fluorouridine, and 5-fluoro-2'-deoxyuridine. Cancer Res 1979;39:2406-13.

39 Bagrij T, Kralovanszky J, Gyergyay F, Kiss E, Peters GJ. Influence of uridine treatment in mice on the protection of gastrointestinal toxicity caused by 5-fluorouracil. Anticancer Res 1993;13:789-93.

40 Codacci-Pisanelli G, Noordhuis P, van der Wilt CL, Peters GJ. Selective protection by uridine of growth inhibition by 5-fluorouracil (5FU) mediated by 5FU incorporation into RNA, but not the thymidylate synthase mediated growth inhibition by 5FU-leucovorin. Nucleosides Nucleotides Nucleic Acids 2008;27:733-9.

41 Tetzlaff ED, Correa AM, Baker J, Ensor J, Ajani JA. The impact on survival of thromboembolic phenomena occurring before and during protocol chemotherapy in patients with advanced gastroesophageal adenocarcinoma. Cancer 2007;109:1989-95.

42 Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol 2007;25:3217-23.

43 Yoshida M, Ohtsu A, Boku N, Miyata Y, Shirao K, Shimada Y, et al. Long-term survival and prognostic factors in patients with metastatic gastric cancers treated with chemotherapy in the Japan Clinical Oncology Group (JCOG) study. Jpn J Clin Oncol 2004;34:654-9.