Journal of BUON **14:** 429-433, 2009

ORIGINAL ARTICLE

Efficacy and toxicity of lower dose UFT without leucovorin in metastatic gastric cancer patients

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Summary

Purpose: *Gastric cancer is the 4th most commonly diagnosed cancer and the 2nd leading cause of cancer death worldwide. In this study assessed were the efficacy and toxicity of the combination of epirubicin, cisplatin and UFT in patients with metastatic gastric cancer (MGC).*

Patients and methods: *In this retrospective study 27 patients with MGC were treated with epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 i.v. on day 1 and subsequently UFT 250 mg/m^2/day orally in divided doses for 21 days, followed by a 7-day rest (EP-UFT).*

Results: *Response and toxicity evaluation was possible for 25 patients. Three complete (12%) and 2 partial (8%) responses were observed. With a median follow-up 37 weeks (range 15-117), the median progression-free survival (PFS) and overall survival (OS) were 24 and 31 weeks, respectively. WHO grade 3 or 4 toxicity included neutropenia in 3 (12%) patients and nausea/vomiting in 1 (4%) patient. Neutropenic fever developed in only 1 (4%) patient.*

Conclusion: *EP-UFT with lower UFT doses and without leucovorin support is a safe and effective regimen as first -line treatment of MGC.*

Key words: cisplatin, epirubicin, gastric cancer, metastatic, UFT

Introduction

Gastric cancer is the second leading cause of cancer death worldwide and continues to carry a poor prognosis, making it a therapeutic challenge for oncologists. More than two-thirds of the patients present with advanced stage and median survival does not exceed 9 months despite systemic chemotherapy [1]. Although combination regimens are more beneficial than best supportive care alone [2,3], optimal regimen has remained elusive in the metastatic settings.

In phase III trials for MGC, the most promising regimen is the combination of epirubicin, cisplatin and continuous infusion 5-fluorouracil (5-FU; ECF). This regimen was compared with FAMTX (5-FU, doxorubicin, methotrexate) in a phase III trial, and proved superior to FAMTX in terms of response rate (RR) (45 vs. 21%) and OS (8.9 vs. 5.7 months) [4]. Since the publication of this trial, ECF has become a widely accepted standard regimen in the treatment of MGC. Although newer agents, such as taxanes and topoisomerase inhibitors, have also shown promising activity compared with ECF, these data are not clear as yet. Despite the favorable results, there are some drawbacks. In the docetaxel trial [5] median survival was 9.2 months, and in the irinotecan trial [6] lack of survival advantage was documented compared to cisplatin plus 5-FU combination [5,6].

In ECF, 5-FU is administered as continuous infusion during 21 days, requiring a central venous catheter. UFT (Tegafur and Uracil in 1:4 molar ratio) is an oral prodrug of 5-FU. Oral UFT showed blood concentrations comparable with low dose continuous infusion of 5-FU [7]. The use of oral forms of 5-FU bears some advantages over infusional administration such as decreasing the hospitalization time, eliminating the

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Received 22-09-2008; Accepted 24-11-2008

inconvenience associated with use of infusion pumps, and improving the quality of life (QoL).

In the present study, we aimed to evaluate the efficacy and tolerability of the UFT, epirubicin and cisplatin combination (EP-UFT) (without leucovorin support) in patients with MGC.

Patients and methods

Patient characteristics

From May 2004 to August 2005, 27 patients with MGC were treated in our institution with EP-UFT. All of the patients had histologically confirmed metastatic adenocarcinoma of the stomach.

There was not age limit for patients' inclusion in this study. Patients with history of other cancer, uncontrolled central nervous system metastasis, uncontrolled infectious disease, and severe cardiac disease were excluded from this analysis.

Adequate oral administration capacity, World Health Organisation (WHO) performance status 0-2, life expectancy of over 3 months, and adequate hematological (neutrophil count >1500/mm^3, platelet count >100.000/mm^3), renal (serum creatinine <1.5× the upper normal value-UNV) and hepatic (alkaline phosphatase <3× the UNV, bilirubin <1.5× the UNV, AST-ALT <2× the UNV) functions were the basic criteria for the administration of this regimen.

Baseline biological analyses (blood cell count, serum creatinine, bilirubin, AST, ALT, and alkaline phosphatase) and disease assessment (CT scan) were performed within one week and month, respectively, before the first cycle of chemotherapy. Physical examination and toxicity assessment (complete blood count and serum biochemistry) were performed at the start of each 28-day cycle. The study protocol was approved by the institution ethics committee and conducted according to the Helsinki Declaration guidelines. Written informed consent was obtained from each patient.

Treatment plan

On day 1, epirubicin 50 mg/m^2 i.v. and cisplatin 60 mg/m^2 i.v. infusion with standard hydration and antiemetics were administered. UFT was given orally at least 1 h before meals at a dose of 250 mg/m^2/day in 2 divided doses for 21 days. The treatment was repeated every 28 days. Oral leucovorin was not used. A detailed informational at form was given to all patients for the usage of UFT and they were asked at each follow-up visit whether they had taken the capsules prescribed. Ondasetron, tropisetron or granisetron were administered for antiemetic prophylaxis. Granulocyte colony stimulating factor (G-CSF) was used only if necessary. Doses of all drugs were reduced by 25% in case of grade 3-4 toxicity.

Toxicity and response evaluation

Toxicity was evaluated at each cycle according to WHO toxicity criteria (0- 4). All of the patients had measurable and/or evaluable disease at the baseline evaluation. Tumor response was assessed by CT scan every 3 cycles or earlier if clinically indicated. Responses were evaluated according to the WHO response criteria: complete response (CR) was defined as disappearance of all known lesion(s) confirmed at 4 weeks; partial response (PR) as at least 50% decrease confirmed at 4 weeks; stable disease (SD) as neither PR nor PD; progressive disease (PD) as 25% increase or appearance of new lesion(s) [8].

Statistical analysis

Statistical analysis was performed with the SPSS 10 software package program. PFS was calculated from the first day of treatment to evidence of clinically/radiologically disease progression or death. OS was calculated from the first day of treatment to last follow-up or death. Kaplan-Meier method was used for construction of survival curves. Mann-Whitney U test was used for comparison of responses. All differences were considered significant when p-values were < 0.05.

Results

Patients

There were 20 males and 7 females with median age 51 years (range 25-76). The characteristics of these patients are shown in Table 1. Only 5 patients had been previously treated with adjuvant chemotherapy and/or radiotherapy.

Treatment

Response, toxicity and survival evaluations were performed on 25 patients. After the first cycle, 2 patients were lost to follow-up. The total number of treatment cycles was 116 (median 3, range 2-9). Three (12%) of 25 patients required dose reduction by 25% as a result of neutropenia. No patient received second-line chemotherapy.

Toxicity

The most common adverse event was neutrope-

Table 1. Patient and disease characteristics

Characteristic	*Number of patients*	*%*
Sex		
Male/ Female	20/5	
Age (years)		
Median (range)	52 (30- 76)	
WHO performance status		
0 or 1	13	52.0
2	12	48.0
Tumor type		
Signet-ring cell	6	22.0
Well differentiated	18	67.0
Poorly differentiated	3	11.0
Metastatic sites		
Liver	16	64.0
Lung	4	16.0
Peritoneum	3	12.0
Ovary	2	8.0
Lymph nodes	1	4.0
Pleura	1	4.0
Spleen	1	4.0
No. of metastatic organs		
1	23	92.0
≥ 2	2	8.0

nia. WHO grade 3 or 4 toxicities included neutropenia in 3 (12%) patients and nausea/vomiting in 1 (4%) patient. Neutropenic fever developed in only 1 (4%) patient which was easily managed with G-CSF support and antibiotic therapy. Grade 3-4 anemia and thrombocytopenia were not observed. There was no treatment-related death or patient withdrawal because of toxicity. Grade 3-4 toxicities are shown in Table 2.

Response to therapy

Three (12%) CR and two (8%) PR were observed in 25 eligible patients. SD and PD were observed in 5 (20%) and 15 patients (60%), respectively. Median response durations were 74, 28 and 30 weeks in patients with CR, PR and SD, respectively (Table 3).

Table 2. Grade 3-4 toxicities

Toxicity	*Number of patients*	*%*
Neutropenia	3	12.0
Neutropenic fever	1	4.0
Nausea and vomiting	1	4.0
Alopecia	4	16.0

Table 3. Response duration

Response to therapy	*Patients n (%)*	*Response duration (weeks)*
CR	3 (12)	74 (38-115)
PR	2 (8)	28 (25-31)
SD	5 (20)	30 (19-38)

Survival

With a median follow-up 37 weeks (range 15-115), the median PFS and OS were 24 and 31 weeks, respectively (Table 4). In patients with objective response (CR and PR), median PFS and OS were 38 weeks (range 25-115). In the remaining patients (SD and PD), median PFS and OS was 18 (range 8-40) and 30 weeks (range 15-60), respectively (Figures 1 and 2). Median PFS (p=0.005) and OS (p=0.017) were significantly longer in objective responders.

Discussion

In our study EP-UFT regimen, consisting of lower dose of UFT without leucovorin support, showed that

Table 4. Survival data

Median PFS, weeks (range)	24 (8 - 115)
1-year, n (%)	2 (8)
2-year, n (%)	1 (4)
Median OS, weeks (range)	31 (15 - 115)
1-year, n (%)	3 (12)
2-year, n (%)	1 (4)

PFS: progression-free survival.

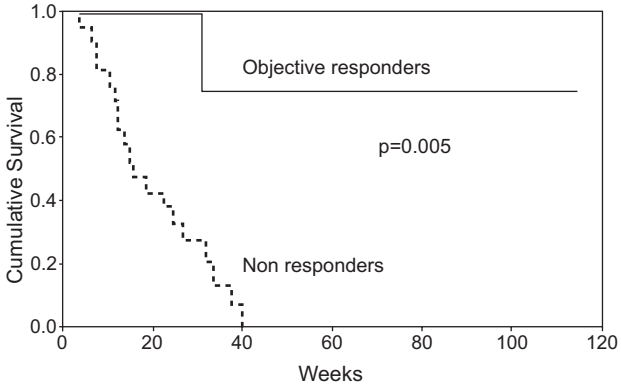

Figure 1. Progression free survival.

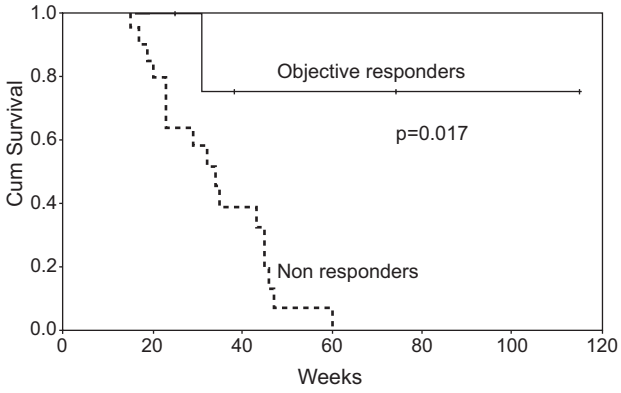

Figure 2. Overall survival.

the combination was fairly active and quite well tolerated as first-line chemotherapy for MGC. Median PFS and OS were comparable with other reported phase II trials, notwithstanding the low overall objective response rate (20%). Furthermore, approximately half of the patients in this study had low performance status.

In a phase I-II study, the efficacy of EP-UFT was evaluated with escalating UFT doses (from 150 mg/m^2/day to 325 mg/m^2/day) [9]. Recommended UFT dose was reported as 200 mg/m^2, and at higher doses more than two-thirds of the patients required dose reductions although mostly for persistent grade 2 nausea, diarrhea or fatigue rather than for severe acute toxicity. Generally, UFT is mostly used at a dose of 300 mg/m^2/day or above with leucovorin support [10,11]. In our study, UFT dose was 250 mg/m^2/day for 21 days while the dose and administration mode of epirubicin and cisplatin were similar to other phase II trials.

Reported overall response rates and survival with EP-UFT were in the range of 38-57.7% and 9-15 months, respectively [9-13]. The highest response rate and median survival were reported by Jeen et al. where all of the 47 patients received epirubicin (50 mg/m^2 on day 1), cisplatin (60 mg/m^2 on day 1) and UFT (360 mg/m^2/day) with fixed dose of leucovorin (45 mg/m^2/day) for 21 days. The majority of the patients (75%) had good performance status and in 36% of them measurable disease was nodal involvement only. Significant grade 3 or 4 toxicity included neutropenia (42%), nausea (27%), vomiting (18%), oral mucositis (6%), and diarrhea (6%) [12].

In another phase II trial, lower dose of UFT (300 mg/m^2/day) with leucovorin support (30 mg/m^2/day) for 21 days resulted in lower response rate (38%) and OS (9.5 months) in 39 MGC patients. In that study, 49% of the patients had metastases in 2 or more organs and 21% of them had low performance status. Significant grade 3 or 4 toxicities included neutropenia (20%), nausea-vomiting (8%), oral mucositis (5%), and diarrhea (8%), and were relatively higher than in our study [10].

Leucovorin has been the drug most commonly combined with 5-FU for biomodulation, however its optimal dose and schedule of administration have not yet been determined. A direct comparison of UFT alone vs. UFT with low- or high-dose leucovorin has not been clinically performed. Although higher doses of leucovorin support (≥150 mg/m^2) were accompanied with increased response rates, UFT with low-dose leucovorin showed similar response rates to those in which UFT was administered alone [14]. Nevertheless, the data support that the addition of leucovorin to UFT gives similar response rates as 5-FU plus leucovorin. The addition of leucovorin to i.v. 5-FU regimens has been evaluated in a number of clinical trials [15,16], and a meta-analysis has demonstrated a significantly higher tumor response rate with the combination compared with the administration of 5-FU alone (23 vs. 11%) [17]. However, this advantage of leucovorin support did not lead to any discernible advantage in terms of survival [15]. In our EP-UFT regimen, UFT dose was relatively lower and leucovorin was not used for biomodulation. These two factors might have influenced our rather low objective response rates. Yet, our survival results were comparable with other trials [10,11]. Improving response rates is an important goal in oncology, but high objective response rates do not always predict the magnitude of PFS or OS benefit. It is important to balance efficacy with the ability of patients to tolerate toxicities that may be associated with some of the more aggressive combinations and to match therapies accordingly [10].

Population characteristics are among the most important factors that may affect results of the different studies significantly. In a multivariate prognostic factor analysis from 3 multicenter, randomized, controlled trials [18], 4 poor prognostic factors were identified: performance status ≥2, liver metastases, peritoneal metastases and high alkaline phosphatase level. The authors have also described a simple prognostic index, dividing patients into good (no risk factor), moderate (1 or 2 risk factors) or poor (3 or 4 risk factors) risk groups. Median survival time and one-year survival according to these risk groups were reported as 11.8, 7.4, 4.1 months and 48.5, 25.7, and 11%, respectively [18]. In our study population, about half of the patients had low performance status and the majority of them had liver metastases.

In conclusion, EP-UFT with lower UFT doses and without leucovorin support is a safe and fairly effective regimen as first-line treatment in MGC. The advantage of outpatient administration and the very low toxicity profile can characterize it as a convenient palliative regimen, especially in patients with poor prognostic factors.

References

1. Kim TW, Kang YK, Ahn JH et al. Phase II study of capecitabine plus cisplatin as first-line chemotherapy in advanced gastric cancer. Ann Oncol 2002; 13: 1893-1898.
2. Wils J. The treatment of advanced gastric cancer. Semin Oncol 1996; 23: 397-406.
3. Glimelius B, Ektrom K, Hoffman K et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol 1997; 8: 163-168.

4. Webb A, Cunningham D, Scarffe JH et al. Randomized trial comparing epirubicin, cisplatin, and fluorouracil, doxorubicin, and methotraxate in advanced eosophagogastric cancer. J Clin Oncol 1997; 15: 261-267.
5. Ajani AJ, Moiseyenko VM, Tjulandin S et al. Clinical benefit with docetaxel plus fluorouracil and cisplatin compared with cisplatin and fluorouracil in a phase III trial of advanced gastric or gastroesophageal adenocarcinoma: The V-325 Study. J Clin Oncol 2007; 25: 3205-3209.
6. Dank M, Zluski J, Valvere V et al. Randomized phase 3 trial of irinotecan (CPT-11) + 5-FU/folinic acid (FA) versus CDDP+5-FU in first-line advanced gastric cancer patients. J Clin Oncol 2005; 23 (Suppl): 16S, 4003 (abstr).
7. Takiuchi H, Ajani JA. Uracil-tegafur in gastric carcinoma: a comprehensive review. J Clin Oncol 1998; 16: 2887-2885.
8. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-214.
9. Seymour MT, Dent JT, Papamichael D et al. Epirubicin, cisplatin and oral UFT with leucovorin (ECU): a phase I-II study in patients with advanced upper gastrointestinal tract cancer. Ann Oncol 1999; 10: 1329-1333.
10. Idelevich E, Karminsky N, Dinerman M et al. Phase II study of cisplatin, epirubicin, UFT, and leucovorin (PELUF) as first-line chemotherapy in metastatic gastric cancer. Acta Oncol 2007; 46: 324-329.
11. Woo IS, Moon DH, Shim BY et al. A phase II study of epirubicin, cisplatin and uracil-tegafur for advanced gastric carcinoma. Jpn J Clin Oncol 2005; 35: 13-17.
12. Jeen YT, Yoon SY, Shin SW et al. Phase II trial of epirubicin, cisplatin, oral uracil and tegafur, and leucovorin in patients with advanced gastric carcinoma. Cancer 2001; 15: 2288-2293.
13. Kim YH, Kim BS, Seo JH et al. Epirubicin, cisplatin, oral UFT, and calcium folinate in advanced gastric carcinoma. Oncology 1999; 13 (7 Suppl 3): 64-68.
14. Sulkes A, Benner SE, Canetta RM. Uracil-Ftorafur: An oral fluoropyrimidine active in colorectal cancer. J Clin Oncol 1998; 16: 3461-3475.
15. Wolmark N, Rockette H, Mamounas E et al. Clinical trial to assess the relative efficacy of fluorouracil and leucovorin, fluorouracil and levamisole, and fluorouracil, leucovorin, and levamisole in patients with Dukes' B and C carcinoma of the colon: results from National Surgical Adjuvant Breast and Bowel Project C-04. J Clin Oncol 1999; 17: 3553-3559.
16. Haller DG, Catalano PJ, Macdonald JS et al. Phase III study of fluorouracil, leucovorin, and levamisole in high-risk stage II and III colon cancer: final report of Intergroup 0089. J Clin Oncol 2005; 23: 8671-8678.
17. Advanced Colorectal Cancer Meta-Analysis Project. Writing committee: Piedbois P, Buyse M, Rustem Y et al. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. Advanced Colorectal Cancer Meta-Analysis Project. J Clin Oncol 1992; 10: 896-903.
18. Chau I, Norman AR, Cunningham D, Waters JS, Oates J, Ross PJ. Multivariate prognostic factor analysis in locally advanced and metastatic esophago-gastric cancer. Pooled analysis from three multicenter, randomized, controlled trials using individual patient data. J Clin Oncol 2004; 22: 2395-2403.