PERGAMON

European Journal of Cancer 37 (2001) 1642–1647

European Journal of Cancer

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# 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

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Received 12 April 2001; accepted 18 April 2001

**Abstract**

A phase II study was performed to evaluate 1-(2-tetrahydrofuryl)-5-fluorouracil and uracil (UFT) and leucovorin as first-line chemotherapy in European patients with advanced gastric cancer. From 38 patients, 25 were evaluable for response and 36 for toxicity. Patients received UFT at 300 mg/m$^2$/day for 28 days, every 35 days and leucovorin at 90 mg/day on an identical schedule. Overall response rate was 10.5% (95% confidence interval (CI): 3.7–22.5%) in intent-to-treat analysis and 16% (95% CI: 5.7–33%) in evaluable patients. Grade 3–4 common toxicity criteria (CTC) toxicities were diarrhoea (28%; 10/36), nausea (11%; 4/36), vomiting (8%; 3/36) and asthenia (11%; 4/36). 23 patients in 44% (42/96) of the courses had to skip days of treatment due to toxicity or to non-compliance. In conclusion, UFT + leucovorin has a definitive, but low, efficacy in advanced gastric cancer patients. Toxicities were mainly gastrointestinal and treatment needs to be withheld if grade 2 diarrhoea occurs. 

*Keywords:* Gastric cancer; Phase II; Chemotherapy; UFT; Leucovorin

## 1. Introduction

Adenocarcinoma of the stomach is one of the leading causes of cancer-related deaths in Japan, Eastern Europe and South America, with a significant decrease of incidence in the United States and Western Europe [1,2]. The prognosis remains extremely poor with a 5-year survival rate ranging from 5 to 15%.

In spite of great surgical efforts, results after resection of gastric carcinoma in a 'curative' approach are dismal and at least 80% of patients develop recurrent and/or metastatic disease. Single drugs with reported response rates between 20 and 36% were 5-fluorouracil (5-FU) [3,4], mitomycin C, doxorubicin and cisplatin. Nevertheless, complete responses were uncommon and responses were generally of brief duration without a significant impact on survival.

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0959-8049/01/$ - see front matter 
PII: S0959-8049(01)00187-3

To improve the response rate and increase survival, combinations of these different drugs were developed. Thus, successive polychemotherapy regimens were initiated: FAM (5-FU, doxorubicin, mitomycin C) [4], FAP (5-FU, doxorubicin, cisplatin) [5], CDDP-5-FU (cisplatin, 5-FU) [6], EAP (etoposide, doxorubicin, cisplatin) [7,8], ELF (etoposide, leucovorin, 5-FU) [9], FAMTX (5-FU, doxorubicin, methotrexate) [8,10] and ECF (5-FU, doxorubicin, cisplatin) [11]. In initial phase II studies, an increase in response rate (40–60%) and in complete response rate (2–15%) has been reported, with no trend of improvement in the median duration of survival, which lasts from 6 to 10 months. At this time, only protocols with FAM or FAM associated with 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) have been compared with single agent 5-FU chemotherapy with no significant increase in the response rate [12,13] or in survival [4,12,13]. Other phase III trials have been conducted to compare polychemotherapy regimens; none has clearly shown a reproducible significant advantage [8,10,11].

Moreover, some of these protocols were associated with a significant increase of toxicity. EAP, and to a lesser extent FAMTX, induced severe toxicity, such as myelotoxicity [7,8,10,11].

The UFT regimen is composed of 1-(2-tetrahydrofuryl)-5 fluorouracil (Ftorafur (FT)) and uracil in a molar ratio of 1:4. FT is converted to 5-FU *in vivo* [14]. The co-administration of uracil enhances the concentration of 5-FU in tumours and the resulting antitumour activity of FT [15]. From *in vivo* studies, UFT resulted in a 5–10 times greater distribution of 5-FU in tumours. UFT is the first agent of the second generation of 5-FU prodrugs that has already been extensively evaluated in metastatic gastric carcinoma in Japan [16]. Given in doses ranging from 300 to 600 mg/day, UFT produced an overall response of 27.7% among 188 evaluable patients with advanced gastric cancer [16].

From these preclinical data and clinical results establishing a shared efficacy with 5-FU, UFT was logically used in combination either with molecules that can modulate the metabolism of UFT such as leucovorin or with other cytotoxic drugs that have already been associated with 5-FU and shown activity in metastatic gastric cancer (doxorubicin, cisplatin, etoposide, mitomycin C) [17–20].

Leucovorin (5,10-CHO-THF) is a potent inhibitor of thymidylate synthase via fluorodeoxyuridine monophosphate through the formation of a covalent ternary complex. Several preclinical and clinical models have indicated that the cytotoxicity of 5-FU could be enhanced by exogenously administered reduced folate. In two consecutive monocentric phase II trials, 16 and 39 patients with metastatic gastric carcinoma have been treated in Korea with UFT (480 or 360 mg/m$^2$/day) [21,22] in conjunction with 'low-dose' leucovorin (25 mg/m$^2$/day for 21 days, every 28 days). Objective response rates were 28.5% (95% confidence interval (CI): 4.9–52.3%) and 27% (95% CI: 15.4–42.9%), respectively. Reported World Health Organization (WHO) grade 3 or 4 toxicities were mainly diarrhoea (43.8%), oral mucositis (12.5%) and nausea and vomiting (12.5%) in the first trial with the higher dose of UFT [21], while severe diarrhoea was significantly reduced to 18% in the second trial with UFT at 360 mg/m$^2$ [22]. Moreover, UFT (300 mg/m$^2$/day) has already been used in metatastatic colorectal carcinoma with 'high-dose' leucovorin (150 mg/day for 28 days, every 35 days) [23,24] or with 'low-dose' leucovorin (75 to 90 mg/days for 28 days, every 35 days) [25,26]. The optimal dosage of leucovorin to produce optimal modulation remains controversial, but the lower dosage allows complete absorption and has been well tolerated. In those trials with 'low-dose' leucovorin, 21 and 13% of patients experienced common toxicity criteria (CTC) grade 3–4 diarrhoea and nausea/vomiting, respectively [25,26].

Based upon the effectiveness of single agent 5-FU in gastric cancer and the results of the abovementioned studies in colorectal cancer, we initiated a multicentric phase II trial with UFT given orally for 28 days in combination with oral 'low-dose' leucovorin in patients with metastatic gastric cancer.

## 2. Patients and methods

### 2.1. Patients

Adults patients were eligible if they had histologically-confirmed gastric cancer with distant metastatic disease that could be measured in two dimensions. Patients had an Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$ and a life expectancy $> 3$ months. No prior chemotherapy was allowed and they were excluded if they had received radiotherapy in the previous 4 weeks. Biological inclusion criteria were absolute neutrophil count $\geqslant 2\times10^9$/l, platelet count $\geqslant 100\times10^9$/l, creatinine concentration and bilirubin level less than 1.5 the upper limit of normal for institutions. Written informed consent was obtained from all patients before entry into the trial.

### 2.2. Pretreatment evaluation

Clinical history and physical examination were recorded for all patients. Before inclusion, patients had a staging including an abdominal computed tomographic (CT) scan and if applicable, other CT scans depending on the metastatic sites. A full blood count and differential, electrolytes, renal and liver functions were checked. All patients had a baseline electrocardiogram (ECG).

### 2.3. Treatment

UFT (Bristol-Myers Squibb, Belgium) was given orally at 300 mg/m$^2$ for 28 consecutive days. The total daily dose was divided into three doses, given every 8 h. The total daily dose of UFT was rounded to the nearest 100 mg. Leucovorin was given orally at 90 mg, divided into three doses, given every 8 h with each dose of UFT for 28 consecutive days. UFT and leucovorin were given daily for 28 days, followed by a 7-day rest. The following cycle was scheduled on day 36.

### 2.4. Dose modification

Due to the toxicity seen during or between cycles, the dose could be modified. Toxicity was graded using the CTC.

During a cycle of treatment, if a grade 3 CTC toxicity for granulocytes or platelets was noted, UFT and leucovorin treatment was withheld until the granulocyte level returned to $\geqslant 1.5\times10^9$/l and the platelet count returned to $\geqslant 100\times10^9$/l. Following recovery, UFT was reduced by 50 mg/m$^2$/day. If any non-haematological toxicity $\geqslant$CTC grade 2 occurred, except untreated anaemia, inadequately treated nausea or vomiting, alopecia and asthenia, UFT therapy was withheld until the toxic event had completely resolved or returned to baseline. Therapy was started again at the same dose level if the toxicity was no more than CTC grade 2. In case of toxicities of CTC grade 3 or 4, therapy was resumed at a reduced UFT dosage of $-50$ or $-100$ mg/m$^2$/day, respectively. When therapy was withheld due to toxicity during a cycle, those days were counted as treatment days, as UFT was stopped on day 28 of each cycle, irrespective of prior temporary interruptions.

As the start of a new cycle of treatment, dose adjustment was based on the highest toxicity observed during the previous cycle of treatment. The initiation of a new cycle of treatment with UFT plus leucovorin was delayed until absolute neutrophil count $\geqslant 1.5\times10^9$/l and platelet count $\geqslant 100\times10^9$/l. Non-haematological toxicities had to return to CTC grade 1 or to baseline.

### 2.5. Evaluation of treatment

Response was assessed every 10 weeks. Work-up was identical to the initial pretreatment evaluation.

Complete response (CR) was defined as the complete disappearance of all measurable and assessable tumour sites for at least 4 weeks. Partial response (PR) was considered to be a $\geqslant 50\%$ decrease in the sum of products of the greatest perpendicular diameters that lasted at least 4 weeks with no increase in known lesions and without the appearance of any new lesions. The duration of CR and PR was calculated from the first day of treatment. When the evaluation showed a decrease in lesions less than 50% and an increase less than 25%, patients were considered to have stable disease (SD). Progressive disease (PD) was defined as any lesion increasing by greater than 25% or the appearance of a new lesion. When the progression was observed between the completion of the first and the second cycles after entry into the study, patients were considered as an early progression. Patients documented to have a progression prior to 5 weeks after entry into the study were considered non-evaluable for tumour response.

## 3. Results

### 3.1. Patients' characteristics

From July 1997 to December 1997, 38 patients with metastatic gastric carcinoma were entered into the study. 36 patients were assessable for toxicity, while 2 patients died before starting treatment. 13 patients were considered non-evaluable for tumour response: 1 had no measurable lesion, 2 died before treatment, 6 never received a full first cycle or were progressive within the first 5 week cycle and 4 never had an evaluation [lost to follow-up (1), clinical PD (1), death (1), no evaluation (1)]. Median age was 64 years (range 43–76 years). 24 males and 14 females entered the study. Most patients had an ambulatory performance status: 14 patients (37%) had an ECOG performance status of 0, while 19 (50%) had a status of 1 and 5 (13%) had a performance status of 2. All tumours were adenocarcinoma including 3 patients with signet ring-cell carcinoma. 24 patients (63%) underwent prior surgery. 17 patients (45%) had liver metastases, while 14 (37%) had lymph nodes localisation and 9 (24%), 7 (18%) and 3 (8%) patients had a primary recurrence, soft tissue and lung metastatic sites, respectively.

### 3.2. Administration of treatment

The 36 treated patients received a total of 96 courses of treatment. The median number of cycles delivered was 2 (1–12). While 78 (81%) courses were given at a full dose of UFT, 18 (19%) had to be decreased to 250 mg/m$^2$/day for 5 patients (14%), due to CTC grade 3 diarrhoea (3 patients), grade 3 vomiting (1 patient) and grade 3 neutropenia (1 patient). Moreover, 23 patients for a total of 42 courses (44%) interrupted the daily planned schedule because of toxicity (18 courses, 14 patients) including diarrhoea (10 patients), vomiting (3 patients) and asthenia/anorexia/constipation (1 patient). 9 patients were reported not to have taken all the pills planned for a 28 days cycle for less than 5 days during 24 courses, due to missing or for unknown reasons.

### 3.3. Toxicity

Toxicities encountered were evaluated according to the CTC grading system (Table 1). The main toxicities were diarrhoea (21 patients), nausea (20 patients), vomiting (11 patients), asthenia/malaise (8 patients) and stomatitis (6 patients). During 96 courses, 30 grade 3 (grade 3) and 4 (grade 4) events were reported for 36 patients. There were predominantly diarrhoea (grade 3: 7 courses; grade 4: 3 courses), nausea (grade 3: 4 courses), vomiting (grade 4: 3 courses), asthenia (grade 3: 2 courses; grade 4: 2 courses). No skin toxicity and no stomatitis grade 3 or 4 were seen. No toxic death was observed. Despite at least CTC grade 2 haematological or non-haematological toxicities, UFT/leucovorin was not withheld in 15 patients as early as previously planned in the protocol. Toxicities that were not taken into account to withhold drugs were mainly diarrhoea in 11 patients (worse CTC grade 4: 2 patients, grade 3: 5 patients, grade 2: 4 patients). Other toxicities involved were vomiting (CTC grade 4: 1 patient), stomatitis (CTC grade 2: 1 patient), infection (CTC grade 2: 1 patient), infection (CTC grade 2: 1 patient) and dyspnoea (CTC grade 2: 1 patient). 3 of these patients who presented diarrhoea were taken off study due to the toxic events. 4 other patients had a reduced dose on the following courses.

### 3.4. Response to treatment and survival

Among 25 evaluable patients, one CR and three PRs were achieved. 6 patients had stable disease. In intent-to-treat analysis, the objective response rate was 10.5% (95% CI: 3.7–22.5%) and was 16% (95% CI: 5.7–33%) for the evaluable patients. Efficacy was seen on the liver, retroperitoneal lymph nodes, soft tissue and para-oesophageal mass. The median duration of objective response and stabilisation was 187 days (98–419$^+$ days), with a duration of complete response for 358 days. The median time to progression was 69 days (7–358).

Table 1
Toxicity of treated patients ($n=36$): maximum common toxicity criteria (CTC) grade

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Diarrhoea | 6 | 5 | 7 | 3 |
| Nausea | 5 | 11 | 4 | |
| Vomiting | 4 | 4 | | 3 |
| Asthenia/malaise | 3 | 1 | 2 | 2 |
| Pain | 2 | 1 | 1 | |
| Alopecia | 3 | | | |
| Dyspnoea | | 1 | | 1 |
| Infection | | 1 | 1 | |
| Skin | | 1 | | |
| Constipation | 1 | | | |
| Thrombosis | | | 1 | |
| Oedema | | 1 | | |
| Headache | 1 | | | |
| Neurosensory | 1 | | | |
| Anaemia | 22 | 8 | | |
| Neutropenia | 1 | | 1 | |
| Thrombocytopenia | 4 | | | |
| Other | 3 | 6 | 1 | 1 |

## 4. Discussion

The regimen of UFT + leucovorin used in this study showed a definitive efficacy in metastatic gastric cancer, but lower than was expected from previous trials. A large number of phase II studies with UFT alone conducted in Japan have shown an overall response rate of 27.7% [16]. Only two studies [27,28] in this pooled analysis [16] showed a response rate lower than 20% for 41 treated patients, while the response rate varied from 23 to 50% in nine other studies including 147 patients [16]. A single study was performed in Europe with UFT alone in advanced gastric cancer and showed a 6% response rate (95% CI: 0.27–30.2%) in 16 patients [29].

More recently, two consecutive monocentric studies performed in Korea showed efficacy in advanced gastric cancer when UFT was associated with leucovorin with a similar response rate of 27 and 28.5% [21,22].

Moreover, studies of UFT in combination with known active drugs in metastatic gastric carcinoma where UFT replaced 5-FU showed the expected activity of the polychemotherapy was maintained, when considering objective response rate. UFT in association with cisplatin showed a response rate of 42.9% in 14 evaluable patients [17], while the combination of UFT, cisplatin with mitomycin C and etoposide [18] or with doxorubicin and etoposide [19] gave response rates of 54.8 and 40%, respectively. In one trial, where leucovorin was added to UFT in combination with etoposide, the response rate was 35% with four CRs in 46 treated patients [20].

Nevertheless, our study and the other European study are consistent with a definitive, but lower, activity of UFT in patients included in Europe with an advanced gastric cancer [29]. The population of patients entered in the European and the Korean studies were different especially for the sites of metastases and the presence of measurable disease, and that could have affected the response rate. The population profile of patients entered in the two European studies was identical with patients mainly having an ECOG performance status of 0 or 1 and metastases located in the liver (61%, 44.7%) or in the abdomen. In the two consecutive trials carried out in Korea, 31% in the first trial and 35.6% in the second trial had locoregional recurrence without distant metastasis, respectively [21,22]. Moreover, only 28.6 and 28.2% of the evaluable patients had liver metastases,

respectively [21,22]. In the latter study, only 51.3% of the patients had a measurable disease. As most of studies had different dosages and schedules of UFT [16–22,29], it is unlikely that the dosage and schedule of UFT in this trial affected the response rate.

A major concern in this study was the number of patients that could not be evaluated for response. A part of the answer was that patients with metastatic gastric carcinoma may have extremely rapid evolution, at least in the 5 weeks of the first cycle with UFT + leucovorin, while patients were not considered in the design of the protocol to be evaluable. The other point is that the evaluation of response was initially planned at 10 weeks, while it could be necessary in this disease at a metastatic stage to perform an earlier evaluation (at 5 weeks) to handle progression status if present.

Side-effects encountered in this study were mainly digestive, with approximately 58.3% of patients having experienced diarrhoea and approximately 27.8% having a CTC grade 3 or 4 diarrhoea, while in other studies with oral UFT and 'low-dose' leucovorin, either in metastatic gastric or colorectal cancer, 17.9, 18 and 21% of patients had WHO grade 3 or 4 diarrhoea [22,25,26]. The increase of severe diarrhoea seen in this trial should be weighted by the fact that eleven of 21 patients who reported diarrhoea did not have a prompt discontinuation of UFT at the onset of grade 2 diarrhoea, as planned in the guidelines of the protocol. With regard to other toxicities as nausea, vomiting, asthenia and neutropenia, these were present in identical frequency as in recent trials [22,25,26].

In our study, 64% (23/36) of patients in 44% (42/96) of courses had skipped treatment days, in part due to toxicity (39% (14/36) of patients, 19% (18/96) of courses) or to non-compliance mainly for less than 5 days, while in a similar phase II study done in Korea, the interruption of treatment due to toxicity was less frequent (21.6% of patients) [22].

## 5. Conclusion

In this study, UFT and leucovorin showed a definitive, but a low, efficacy in patients with metastatic gastric cancer. The more frequent toxicities were diarrhoea, nausea, vomiting and asthenia, while the main grade 3 and 4 CTC toxicities were diarrhoea, nausea and vomiting. The results showed that UFT at 300 mg/m$^2$/day for 28 days in combination with leucovorin, followed by 1 week rest is a safe schedule for most patients with advanced gastric cancer, but needs to be withheld when at least CTC grade 2 gastrointestinal toxicity occurs. The efficacy of UFT provides a rationale to continue UFT and folinic acid development in association with other drugs in advanced gastric cancer.

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