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Original Paper

Efficacy of Oral Tegafur Modulation by Uracil and Leucovorin in Advanced Colorectal Cancer. A Phase II Study

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A phase II study was performed to assess the efficacy and toxicity of UFT (tegafur–uracil in the molar ratio 1 : 4) modulated with leucovorin (LV) in previously untreated patients with advanced colorectal carcinoma (CRC). 79 patients with measurable advanced colorectal cancer (CRC) and no prior chemotherapy were included. 75 patients were evaluable for toxicity and response. The regimen consisted of LV 500 mg/m^2 administered intravenously on day 1, followed by oral UFT 390 mg/m^2 on days 1–14. Patients received oral LV 15 mg every 12 h on days 2–14. Treatment was repeated every 28 days for a minimum of four courses per patient. Three hundred and ninety-eight cycles of chemotherapy were delivered (median five per patient). 7 patients (9%) had a complete response, and 22 a partial response for an overall response rate of 39%. Mild gastrointestinal toxicity was dose limiting: grade 3–4 diarrhoea appeared in 9% of patients. Other grade 3–4 toxicities were nausea/vomiting and mucositis in 4% of patients, gastric pain and leucopenia in 3%. Oral UFT modulated by oral LV is active in advanced CRC and can be administered on an outpatient basis with no significant toxicity requiring hospitalisation. Given its excellent tolerance profile and low toxicity, the regimen should be thoroughly studied and compared with 5-fluorouracil modulated by LV.

Key words: colorectal, tegafur, uracil, leucovorin, modulation, chemotherapy
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INTRODUCTION

THE ONLY chemotherapy used for advanced colorectal cancer (CRC) for many years has been 5-fluorouracil (5FU), with a response rate of 15–20% [1]. In the last decade, biochemical modulation of 5FU with leucovorin (LV), interferon and *N*-(phosphonacetyl)-L-aspartate has been reported to increase the response rate to 30–40% [2]. In spite of this progress, chemotherapy does not improve survival and produces significant toxicity (diarrhoea and mucositis) [3], so that it remains exclusively palliative. Palliation should be achieved with minimal toxicity and avoiding hospitalisation whenever possible, to preserve the patient's quality of life.

UFT contains 1-(2-tetrahydrofuryl)-5-fluorouracil (tegafur) and uracil in a molar ratio of 1:4. Following activation of tegafur to 5FU by thymidine phosphorylase, uracil inhibits the catabolism of 5FU by competitive inhibition of uracil dehydrogenase. This inhibition predominates in tumoral cells over normal tissues, so that the combination increases the tumour concentration and antineoplastic activity of 5FU [4, 5]. In addition, 5FU remains in the cell for a longer period when given as UFT [5, 6] and some authors have suggested that it could act as a "depot" 5FU [7]. These characteristics, along with the possibility of oral administration, make this cytotoxic drug an interesting choice for the therapy of digestive neoplasms.

The reason why LV modulates and thereby enhances the activity of 5FU has been well described [8, 9]. Several randomised trials have confirmed the advantage of 5FU modulated with LV over 5FU alone [10, 11]. However, after a decade of trials, the optimal dose or scheme, or even the best route of administration of LV remain undefined [12]. Some authors use oral LV with similar efficacy to that achieved with intravenous

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(i.v.) LV [13, 14]. Oral administration offers an additional advantage: the selective absorption of the biologically active L-isomer by the gastrointestinal tract. Thus, the potential side-effects of the D-isomer (which accumulates after i.v. treatment) may be avoided. The plasma levels of LV obtained either by continuous i.v. infusion or orally are comparable, but with a lower level of D-isomer following oral administration [15].

Considering these factors, we developed a scheme of chemotherapy for ambulatory patients with advanced CRC, based on oral administration of UFT modulated with LV. This regimen has been described elsewhere [16]. Briefly, a high dose of i.v. LV is followed by the oral intake of UFT, and oral LV is taken twice daily to maintain the folate deposits and the modulation of 5FU metabolites.

In a phase I trial, we established that the maximal tolerated daily dose of UFT modulated with LV in this manner was 390 mg/m^2, and the dose-limiting toxicity was gastrointestinal [16]. The aim of the present study was to determine the efficacy and toxicity of the regimen.

PATIENTS AND METHODS

From October 1991 to May 1993, 79 patients with metastatic CRC were entered into the study. All had histologically confirmed advanced CRC. The disease was measurable in all cases, i.e. there was at least one lesion bidimensionally measurable by computed tomographic scan or ultrasound; pleural effusion, ascites, bony lesions or previously irradiated lesions were not accepted as measurable disease. Patients who had undergone radiotherapy were eligible, provided that there was at least one measurable lesion outside the radiation field. We excluded patients with resectable hepatic metastases.

Eligible patients had no previous chemotherapy; performance status of 2 or better, according to Zubrod's scale [17]; age < 75 years; adequate bone marrow function defined by a granulocyte count of 2 × 10^9/l or greater, and a platelet count > 100 × 10^9/l; normal renal function, as defined by a serum creatinine level < 115 μmol/l and creatinine clearance > 60 ml/min; adequate hepatic function, that is, serum bilirubin < 35 μmol/l, serum glutamic oxalacetic transaminase and serum pyruvic transaminase levels less than three times the upper normal limit.

The study regimen (Table 1) consisted of LV 500 mg/m^2 in 2 h on day 1, followed by oral UFT, 390 mg/m^2/day in two doses for 14 days. On day 2, patients were given oral LV, 15 mg/12 h for 13 days. The pills were taken before meals to favour absorption (for instance, at 7 a.m. and 7 p.m.). Courses were repeated every 28 days for a minimum of four per patient, unless progressive disease was detected. If the neutrophil count was < 1.5 × 10^9/l or the platelets < 100 × 10^9/l, treatment was postponed for a maximum of 2 weeks. After that time, if the neutrophils were 1–1.5 × 10^9/l or the platelets were 70–100 × 10^9/l, the dose of UFT was reduced by 50% and if lower values resulted, chemotherapy was discontinued. In instances of grade 3–4 non-haematological toxicities, the dose of UFT was reduced by 25% in subsequent courses.

Table 1. Treatment scheme

	Treatment
Day 1	Leucovorin 500 mg/m^2 i.v. UFT 195 mg/m^2/12 h p.o.
Days 2–14	Leucovorin 15 mg/12 h p.o. UFT 195 mg/m^2 12 h p.o.
Cycles	Every 28 days

p.o., oral; i.v., intravenous; UFT, tegafur–uracil.

Measurable disease, assessed by radiological and/or ultrasound examinations, was documented before entry into the study: in 68 patients, a computed tomography (CT) scan was performed, whereas ultrasound examination was used in 11 patients with only multiple liver metastases. Response was evaluated at the end of every four cycles with a clinical history, physical examination, laboratory studies (as indicated by the initial alterations) and the methods of diagnostic imaging used to measure disease at diagnosis. Response was evaluated by using World Health Organization (WHO) guidelines [18]. Re-evaluation was undertaken sooner if there was clinical evidence of progression. Complete response (CR) required the total disappearance of all tumours initially observed (determined by two observations not less than 4 weeks apart), with no evidence of new areas of malignant disease. Partial response (PR) was defined as a reduction of at least 50% in the sum of the products of the longest perpendicular diameter of all clearly measurable tumour masses (two observations not less than 4 weeks apart), with no increase in the size of any lesion and no new areas of malignant disease. Stable disease was defined as a decrease in total tumour size of less than 50% or a less than 25% increase in the size of one or more measurable lesions. Progression was defined as a 25% increase in any measurable lesion, the appearance of new areas of malignant disease or symptomatic deterioration of the performance status by more than one level. Death due to disease progression or toxicity occurring before those dates were considered as a therapeutic failure. Response duration and survival were calculated from the first day of therapy until the day of death or last known follow-up. Patients who responded were maintained on chemotherapy until progression.

Toxicity for each course was registered before the next treatment course and graded according to WHO criteria [18]. Occasionally, the patients suffered gastric pain related to the ingestion of UFT, but the WHO scale does not include this adverse effect. We considered it to be grade 3–4 if the symptoms were intense enough to require the withdrawal of UFT in spite of the administration of anti-acids or H_2-blockers.

Wilcoxon rank-sum statistics were used to compare quantitative variables and χ^2 for percentages. Survival and the duration of response were calculated using the Kaplan–Meier method.

RESULTS

Patient characteristics

79 patients with advanced CRC were included in this trial. 4 patients (5%) were ineligible: 2 moved to different cities where therapy was changed and 2 had received previous chemotherapy. Table 2 outlines pretreatment characteristics of the 75 evaluable patients.

A total of 398 cycles of chemotherapy was delivered, with a median of five per patient and a maximum of 18 (1 patient). 7 patients received 10 or more courses. The mean dose of UFT was 347 mg/m^2 per cycle, which corresponds to 89% of the projected total dose. 4 patients died in the first 4 months, 3 due to tumour progression and 1 due to a cardiac arrest, apparently not related to therapy.

Response

7 patients (9%) achieved a CR and 22 (29%) a PR. The overall response rate (CR + PR) was 39%, 95% confidence

Table 2. Patient characteristics

	No. (%)
Sex	
Male	41 (55)
Female	34 (45)
Mean age years	57.5 (32–75)
Location of primary tumour	
Colon	49 (65)
Rectum	26 (35)
Performance status	
ECOG 0	10 (13)
ECOG 1	36 (48)
ECOG 2	29 (39)
Number of metastatic sites	
1	52 (69)
2	20 (27)
3	3 (4)
Location of confirmed metastases	
Liver only	35 (47)
Liver and lung	5 (7)
Liver and other sites	11 (15)
Pelvis	12 (16)
Lung only	2 (3)
Lung and other sites	7 (9)
Other	3 (4)

Table 3. Therapeutic results

	No. (%)
Complete response	7 (9)
Partial response	22 (29)
Stable disease	20 (27)
Progression	26 (35)

limit 27.8%–50% (Table 3). When analysed according to the metastatic sites, the response rates were as follows: 46% for those located only in the liver, 37.5% for those in the liver plus any other organ, and 33% for pelvic disease. Only 1 of the 9 patients with metastatic lung involvement responded. The median overall survival was 13.5 months (17 months for patients obtaining CR or PR patients and 9.5 for non-responders). The median response duration was 10 months. None of the patients who achieved a PR after four courses reached a complete remission with subsequent therapy.

The performance status significantly affected the overall response rate (51% for ECOG 0–1 and 22% for ECOG 2, $P < 0.01$). The primary location (rectum or colon), age (more or less than 60 years) and sex did not modify the response rate.

Toxicity

Toxicity, most commonly gastrointestinal, was minimal (Table 4). There was grade 1–2 diarrhoea in 8.5% of the cycles and grade 3–4 in 3.5%. Grade 1–2 nausea/vomiting occurred in 7% of the courses and grade 3–4 in 1%. Other adverse effects (anaemia, leucopenia, cutaneous lesions) appeared in less than 2% of the cycles. 3 patients (4%) required hospitalisation due to grade 3–4 diarrhoea (1 had to receive somatostatin analogue) and one also had grade 4 leucopenia. There were no toxic deaths. The dose of UFT was reduced to 300 mg/m^2 in the 10 patients (13%) with grade 3–4 toxicity.

DISCUSSION

In the last few years, increasing interest in the use of oral fluoropyrimidines modulated with LV for the therapy of advanced CRC has emerged. Several phase I studies have been reported, all with doses and schemes different from ours: UFT was given continuously at a dose of 350 mg/m^2/day for 28 days, resting 7 days, and LV was exclusively administered orally, at a dose of 15 mg/day [19] or 150 mg/day [20–22]. Two recent phase II trials used this scheme. The global response rate obtained with UFT plus a low dose of LV (15 mg/day) was 25% [23], whereas it was 42% with higher doses (150 mg/day) [24].

In our scheme, the oral administration of LV was preceded by the i.v. infusion of high doses of LV to maximise the cellular deposits of folate. This is based on *in vitro* observations which suggest that the optimal stabilisation of the ternary complex and potentiation of 5FU cytotoxicity is achieved at a total LV concentration of 20 μmol/l in tumoral tissue [8]: such a concentration is only achievable with high doses of LV, for instance 500 mg/m^2 of LV in 2 h [25]. The intracellular metabolism of LV produces polyglutamate forms, which give rise to a stable ternary complex. This complex (LV derivatives + thymidylate synthase + 5-fluorodeoxyuridine monophosphate, a 5FU derivative) remains within the cell for substantial periods [26–31]. A study has shown that the longer the exposure to LV, the more efficient the metabolism of LV [29]. In summary, the

Table 4. Toxicity (398 cycles)

	WHO grade 1–2		WHO grade 3–4	
	Per patient No. (%)	Per cycle No. (%)	Per patient No. (%)	Per cycle No. (%)
Nausea/vomiting	15 (20)	29 (7)	3 (4)	3 (1)
Diarrhoea	10 (13)	34 (9)	7 (9)	14 (4)
Mucositis	4 (5)	9 (2)	3 (4)	5 (1)
Gastric pain	8 (11)	12 (3)	2 (3)	2 (1)
Skin	2 (3)	2 (1)	1 (1)	1 (1)
Anaemia	2 (3)	6 (2)	—	—
Excessive lacrimation	2 (3)	2 (1)	—	—
Leucopenia	1 (1)	2 (1)	2 (3)	3 (1)

administration of LV should be prolonged or repetitive in order to expand the intracellular exposure to the ternary complex. In our scheme, the aim of the oral administration of LV was to maintain maximum cellular deposits during UFT administration and therefore to obtain continuous modulation.

The combination we designed may comply with these theoretical requirements to effectively modulate UFT metabolites. The high response rate, comparable with the more active regimens against advanced CRC [2], supports this suggestion.

In spite of these theoretical considerations, recent studies show that the activity of thymidylate synthase in untreated human tumours varies widely [32], which justifies the fact that a concentration of 1 μmol/l of LV was found to be enough in one study [33]. This concentration may be achieved with an oral dose of 150 mg/day of LV, such as that used by Pazdur *et al.* [24]. However, the patient has to take many pills in that scheme, which could affect his/her compliance with therapy. Saltz and colleagues used lower doses of LV [23] and, although the dose of UFT remained the same, they obtained a lower response rate (25%, 95% confidence interval 6–44%). Saltz's series is very small so it has a broad confidence interval, but its results may indicate that low doses of LV do not efficiently modulate UFT. In the absence of direct randomised comparisons between these three schemes, it is impossible to determine the superiority of one regimen over another.

In our series, a good performance status and the exclusive hepatic metastases were related to a higher response rate. These observations have also been outlined by other authors [29]. It could be argued that, in our series, there was a favourable distribution of prognostic factors. However, our patients had similar characteristics to those of other series [11, 31, 34] and came from different cities, so that they reflect the general features of patients with advanced CRC. For all these reasons, we considered that the favourable results obtained could be attributed to the treatment.

The toxicity of the present scheme, as with most combinations using 5FU and LV, was mainly gastrointestinal: diarrhoea, nausea/vomiting and mucositis. However, diarrhoea was rather less frequent in ours than in other series with 5FU–LV (continuous infusion [35, 36] or bolus [3, 31, 37]): grade 3–4 diarrhoea appeared in 9% of the patients, whereas this percentage was approximately 20% in most series [3, 11, 31]. Myelotoxicity was exceptional. When the therapy for a tumour is exclusively palliative, it is important to preserve quality of life by using active and minimally toxic regimens. The present combination seems to meet these goals. These characteristics make our scheme a good basis from which to determine more complex regimens that might increase efficacy. In fact, as 60–70% of patients with advanced CRC do not respond to 5FU modulated with LV, better results could be achieved by incorporating drugs with a different mechanism of action: cytokines and other cytostatics or modulators. Finally, the oral administration of chemotherapy allows considerable savings, because it avoids hospitalisation and the use of infusion pumps in the treatment of one of the most prevalent neoplasms.

In summary, the combination of UFT–LV shows considerable activity in advanced CRC. We believe that its selectivity and efficacy should be compared with those of 5FU–LV in a randomised phase III trial.

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