UFT in combination with oxaliplatin: clinical phase I study in patients with advanced or metastatic solid tumors

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This phase I trial evaluated the combination of oxaliplatin plus UFT in patients with advanced solid tumors to determine the maximum tolerated dose (MTD) and the dose limiting-toxicity for future phase II trials. Eligible patients ($N=27$) were treated in sequential cohorts of three to six patients. The starting doses for oxaliplatin and UFT were 70 mg/m^2 and 250 mg/m^2/day respectively, and five dose levels were designed up to 85 mg/m^2 and 400 mg/m^2/day. Oxaliplatin was administered i.v. on day 1 and 15, and oral UFT was given daily in three divided doses on days 1–21 followed by 1 week rest of a 28-day cycle. At the recommended dose, six additional patients were entered. In total, 79 courses were administered with a median of 3 (range 1–6). MTD was not reached; oxaliplatin 85 mg/m^2 on day 1 and 15 plus UFT 400 mg/m^2/day for 21 days was considered the optimum combination for phase II trials. Gastrointestinal toxicity and asthenia were the most common adverse events. Eight out of 13 patients (61.5%) with metastatic colorectal cancer achieved stable disease. UFT plus oxaliplatin is a feasible and safe combination. A phase II trial in first-line advanced colorectal cancer is ongoing. *Anti-Cancer Drugs* **17:417–421 © 2006 Lippincott Williams & Wilkins.**

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Introduction

5-Fluorouracil (5-FU)/folinic acid-based combinations remain the cornerstone of treatment for patients with metastatic colorectal cancer. Although administration is inconvenient and expensive, continuous infusion of 5-FU induces better outcomes [1]. An alternative approach to optimizing 5-FU-based therapy has been the development of oral fluoropyrimidine derivates. UFT is composed of tegafur [1-(2-tetrahydrofuryl)-5-fluorouracil] and uracil in a molar ratio of 1:4. After oral administration, tegafur is rapidly absorbed and metabolized to 5-FU. Uracil is a competitive inhibitor of didydropyrimidine dehydrogenase leading to increased and sustained serum levels of 5-FU [2]. A double-blind comparison of plasma fluorouracil concentrations after oral UFT and continuous infusion 5-FU showed no differences between the two routes in terms of area under the curve, suggesting an equivalence between them [3]. A synergistic effect of the combination of UFT and oxaliplatin has been demonstrated in the HT29 cell xenograft model [4].

Recently, Chen *et al.* carried out a phase I study in patients with advanced gastric cancer to determine the recommended dose of the combination of oxaliplatin plus UFT modulated by leucovorin [5]. With a fixed-dose of UFT 300 mg/m^2/day and leucovorin 60 mg/day on days 1–21, the maximum tolerated dose (MTD) for oxaliplatin was 100 mg/m^2 days 1 and 15 of a 28-day cycle. However, a phase II trial conducted by Feliu *et al.* in patients with metastatic colorectal cancer reported a high gastrointestinal toxicity when oxaliplatin 85 mg/m^2 on days 1 and 15 was combined with UFT 390 mg/m^2 on days 1–14 plus leucovorin in a 28-day cycle [6]. Therefore, we decided to determine the MTD of the combination of a fixed-dose of oxaliplatin 85 mg/m^2 on days 1 and 15 (but adding a first step with 70 mg/m^2 for safety reasons) plus UFT at escalated dose levels. In spite of the Feliu *et al.* experience, where they had to reduce the UFT dose to 300 mg/m^2, we decided to establish a maximum dose level of UFT 400 mg/m^2 because of the omission of leucovorin modulation and our previous experience in a phase II study in colorectal cancer patients treated with UFT monotherapy 400 mg/m^2/day continuously [7]. This UFT schedule appeared active and well tolerated. The results of this phase I trial are presented here.

Patients and methods

Patients enrolled onto the study had histologically proven advanced solid tumor having previously failed standard treatment or for whom no established curative therapy

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exists; age >18 years old; life expectancy of at least 12 weeks; ECOG performance status (PS) 0–1; adequate bone marrow reserve (absolute neutrophil count $>2000/mm^3$, platelet count $>100\,000/mm^3$); adequate renal and hepatic function [serum creatinine $<1.5\times$ upper limit of normal range (ULN), serum bilirubin $<1.5\times$ ULN and serum transaminases $<2.5\times$ ULN]. A washout period since previous chemotherapy or radiotherapy of 4 weeks was required. Exclusion criteria included previous exposure to oxaliplatin or any fluoropyrimide derivate; known hypersensitivity to platinum derivates; presence of central nervous system metastases; serious or non-controlled concurrent medical illness; peripheral neuropathy WHO grade >2 at the study entry and history of other malignancies except *in situ* cervical carcinoma or basal/spindle cell carcinoma of the skin.

The study was approved by independent ethics committees of all participant centers and was conducted in accordance with the Spanish statutes regulating clinical trials. Written informed consent was required.

Treatment protocol and study endpoint definitions

Oxaliplatin was diluted with 500 ml of dextrose 5% and administered i.v. in 2–6 h on days 1 and 15 of a 28-day cycle. UFT was given daily in three divided doses on days 1–21 followed of 1 week rest of a 28-day cycle. The total daily dose was rounded up or down to the nearest 100 mg. Patients should not consume any food for 1 h prior and 1 h after UFT ingestion following the recommendation of Damle *et al.* [8]. The starting doses for oxaliplatin and UFT were 70 mg/m^2 and 250 mg/m^2/day, respectively. Five escalated dose levels were designed (Table 1). At least three patients received a complete course of chemotherapy and were fully evaluated for toxicity before proceeding to the next dose level. Intra-patient dose escalation was not permitted. If none of the initial three patients experienced dose-limiting toxicity (DLT), dose escalation continued. If one of the initial three patients developed DLT, then three additional patients were entered at the same dose level. DLT was defined as nausea and or vomiting grade ≥ 3 despite adequate antiemetic therapy (steroids plus 5-HT$_3$ antagonists at investigator criteria); any non-hematological grade ≥ 3 toxicity except for local reaction or alopecia; any hematological toxicity grade ≥ 3 except for neutropenia; grade 4 neutropenia lasting >5 days or febrile neutropenia defined as temperature $\geq 38.5^\circ$C and neutrophil cell count $\leq 1000/mm^3$; inability of the patient to receive $\geq 75\%$ planned UFT dose. MTD was defined as the highest dose that did not cause DLT in more than one patient. At the MTD dose level 6 additional patients were enrolled in order to fully characterize the toxicity profile of this combination. To determine the MTD, the toxicity of the first cycle was evaluated according to the National Cancer Institute Common Toxicity Criteria version 2.0. Tumor response evaluation was recorded by the investigators following the WHO criteria, every 2 cycles, but measurable disease was not mandatory as an inclusion criteria.

Table 1 Dose escalation strategy

Dose level	Oxaliplatin (mg/m^2)	UFT (mg/m^2) in three divided doses
−1	70	250
1	85	250
2	85	300
3	85	350
4	85	400

Pre-treatment and follow-up assessment

Before starting therapy a complete history, physical examination and determination of PS was obtained for each patient. Samples for blood cell counts and biochemistry were performed at baseline and every other week during the treatment. Symptoms, body weight, physical examination, PS and all adverse events were recorded at the beginning of each cycle.

Results

Between August 2001 and March 2003, 34 patients were recruited at four centers, but seven were not eligible (five for early disease progression without completing the first cycle, one poor recovery from palliative surgery before starting chemotherapy and one opted to withdraw during the first cycle). The characteristics of the 27 eligible patients are described in Table 2. Digestive tract tumors were predominant. A total of 79 courses were administered with a median of 3 (range 1–6).

DLT and recommended dose level

Two patients experienced at least one DLT during cycle 1 (Table 3). One patient at level −1 received less than 75% of the planned UFT dose due to intestinal obstruction. At level 3, another patient presented DLT grade 4 diarrhea. None of the first three patients at level

Table 2 Patient characteristics ($n=27$)

Median age [years (range)]	57 (44–77)
Male/female	17/10
Performance status	
0	14
1	12
NA	1
Tumor types	
Colorectal	13
Gastric adenocarcinoma	5
Pancreatic adenocarcinoma	2
Head and neck squamous cell	2
Others	5
Previous chemotherapy regimen	
0	5
1	6
2	10
≥ 2	6
Previous radiotherapy	
Yes	6
No	21

4 presented DLT and six more patients were added to this level. No DLTs occurred in this expanded cohort. In accordance with these findings, oxaliplatin 85 mg/m^2 on day 1 and 15 plus UFT 400 mg/m^2/day for 21 consecutive days, every 28 days, was considered the optimum combination for this schedule.

Safety profile

Table 4 shows the incidence per patient of treatment-related clinical adverse events during all cycles. The most frequent adverse events were paresthesia (71.4%) (mainly cold-related dysesthesia), emesis (64.3%), asthenia (50%) and diarrhea (35.7%). Grade 3 or 4 emesis appeared in five patients (17.8%) as well as grade 3 asthenia (17.8%). Two patients (7%) presented with grade 3 neuropathy and another two with grade 3 or 4 diarrhea. Hematological toxicity was uncommon and always mild. Other less-common non-hematological toxicities such as mucositis, abdominal pain and cutaneous toxicity were mild or moderate. One patient presented grade 2 serum increased bilirubin level.

No toxic deaths were reported during this phase I trial.

Efficacy data

Although efficacy was not a primary objective of the study, 21 out of 27 patients were evaluable for response. Five patients were not evaluable per protocol criteria because they did not receive at least 2 complete cycles of chemotherapy. In one patient, chemotherapy was discontinued after 3 cycles of chemotherapy due to clinical deterioration, but radiologic assessment was not performed. One patient with advanced gastric cancer responded (5%) and 13 patients (61.9%) achieved stable disease. Eight out of 13 patients (61.5%) with metastatic colorectal cancer achieved stable disease, with a median duration of 112 days.

Table 3 Cycle 1 DLT incidence by dose level

Dose level (mg/m^2)	Patients	Patients with DLTs
Oxaliplatin 70 + UFT 250	6	One grade 3 emesis leading to less than 75% UFT planned dose
Oxaliplatin 85 + UFT 250	3	None
Oxaliplatin 85 + UFT 300	3	None
Oxaliplatin 85 + UFT 350	6	One grade 4 diarrhea
Oxaliplatin 85 + UFT 400	9[a]	None

[a]Including six patients of the expanded cohort.

Discussion

Continuous infusion of 5-FU leads to a higher anti-tumor activity compared with bolus administration, but its clinical use has been limited by the significant inconvenience, cost and complications derived from the use of central venous catheters and pumps. However, patient preference for oral therapy has been reported in randomized and non-randomized trials [9,10]. UFT is a 5-FU pro-drug that could mimic the extended circulation time of 5-FU and the activity was shown to be comparable in first-line colorectal cancer treatment when administered with leucovorin [11,12]. The advantage of the biochemical modulation of continuous infusion 5-FU as well as oral fluoropyrimidines remains to be proved. In our experience, leucovorin did not increase the activity of continuous infusion 5-FU or UFT when these drugs were administered at the recommended dose for single agents, but provided more toxicity [7,13–15]. Patients with metastatic colorectal cancer treated with 48-h 5-FU 3.5 g/m^2 by continuous infusion without leucovorin obtained an overall response rate of 38.5% [10], comparable to that reported with different schedules of continuous infusion 5-FU modulated by leucovorin. The GERCOD group reported an overall response rate of 33.7% when high-dose i.v. leucovorin was added to 48-h continuous infusion 5-FU 3–4 g/m^2 [16]. Patients receiving the LV5FU2 regimen achieved a 28.6% response rate in a multicenter trial [17]. A lower overall response rate of 15% was reported by Streit *et al.* with a schedule of low-dose continuous infusion 5-FU for 5 consecutive days plus i.v. leucovorin modulation [18]. When we tried to modulate the weekly 5-FU 3 g/m^2 by continuous infusion with oral leucovorin, severe toxicity was notably increased, leading to a low median dose intensity of 2.2 g/m^2/week. The overall response rate (29%) was even lower than that obtained in our previous study in which 5-FU was not modulated, in a similar patient population [14]. A randomized EORTC study comparing bolus 5-FU plus leucovorin versus high-dose 24-h continuous infusion of 5-FU and versus the same continuous infusion schedule plus leucovorin failed to demonstrate any difference in terms of response rate between the two

Table 4 Incidence of treatment-related adverse events during all treatment cycles (all grades)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3 + 4 [*n* (%)]	Total [*n* (%)]
Neutropenia		5				5 (17.9)
Anemia	6	2	2		2 (7)	10 (35.7)
Thrombocytopenia	8	4				12 (42.9)
Emesis	6	7	5		5 (17.8)	18 (64.3)
Diarrhea	3	5	1	1	2 (7)	10 (35.7)
Paresthesia	15	3	2		2 (7)	20 (71.4)
Mucositis	6					6 (21.4)
Asthenia	1	8	5		5 (17.8)	14 (50)
Abdominal pain	3	1				4 (14.2)

schedules of continuous infusion 5-FU [19]. Occurrence of grade 3 and 4 diarrhea was higher in the modulated group (22 versus 6%). Our own experience in three consecutive phase II studies in which patients received UFT with or without leucovorin suggests that this oral 5-FU pro-drug might be used without modulation. The total percentages of patients free of progressive disease (objective response plus stable disease) were 56, 43 and 58% for patients treated with UFT 300 mg/m^2/day plus leucovorin 150 mg/day, UFT 400 mg/day plus leucovorin 45 mg/day and UFT 400 mg/m^2/day without leucovorin, respectively [7,15]. In the light of these data, this phase I trial combining UFT with oxaliplatin was designed without leucovorin modulation. The MTD for this combination was not reached. Thus, oxaliplatin 85 mg/m^2 day 1 and 15 plus UFT 400 mg/m^2/day for 21 days was established as the recommended dose for phase II trials. Emesis, asthenia and diarrhea appeared as the most clinically relevant adverse events since neurotoxicity was mainly cold-related dysesthesia and only two patients experienced grade 3 neuropathy. This safety profile is similar to that reported in other phase I and II studies published in the literature, including those in which UFT was modulated by leucovorin. A phase II trial conducted by Kim *et al.* [20] using an every-3-weeks schedule with oxaliplatin 130 mg/m^2 plus UFT 350 mg/m^2/day for 21 days (without leucovorin) reported mild sensory neuropathy as the most common adverse event. No severe toxicities were reported except for a case of grade 3 neutropenia. Two Spanish phase II studies in first- and second-line colorectal cancer therapy showed that diarrhea, emesis and neuropathy are the most relevant adverse events of the oxaliplatin/UFT combination. In both studies, UFT was modulated by i.v. leucovorin on day 1 and oral leucovorin thereafter. Oxaliplatin was infused on days 1 and 14 together with UFT/leucovorin from day 1 to 14, in a 28-day schedule [6,21]. In a phase II trial reported by Bennouna *et al.* [22], in which UFT 300 mg/m^2 was given from day 1 to 14 modulated by 90 mg/day of leucovorin and combined with oxaliplatin 130 mg/m^2 every 3 weeks, asthenia appeared as the most frequent grade 3/4 toxicity (15% of patients). In the present study, asthenia occurred in 50% of patients and 18% of them reached grade 3. In a recent phase II study reported by Petriolli *et al.*, in which UFT/leucovorin alternated with oxaliplatin and irinotecan in a 28-day treatment and 1 week rest, grade 4 toxicity did not appear and only diarrhea (29%) reached grade 3 toxicity [23].

Efficacy data in our study are modest (one partial response in a patient with advanced gastric cancer), but most patients had previously received more than one regimen of chemotherapy. Among patients with advanced colorectal cancer, 61.5% achieved stable disease. Kim *et al.* reported a 12.9% response rate and 18% stable disease in 5-FU pre-treated patients with their UFT/oxaliplatin combination [20]. Promising results were obtained by Petriolli *et al.* in first-line chemotherapy [23].

In conclusion, the results of our trial indicate that UFT 400 mg/m^2 for 21 days plus oxaliplatin 85 mg/m^2 on days 1 and 15 is the recommended dose for this combination. Diarrhea, emesis and asthenia are the most relevant adverse events. A phase II trial in first-line chemotherapy for advanced colorectal cancer patients is ongoing.

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