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Phase I trial of UFT/leucovorin and irinotecan in patients with advanced cancer

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Abstract

UFT (BMS-200604, Uftoral®) is an oral fluoropyrimidine that combines uracil and the 5-fluorouracil (5-FU) prodrug, ftorafur, in a 4:1 molar ratio with single-agent activity in breast and gastrointestinal cancers. *In vitro* studies have shown that irinotecan downregulates thymidylate synthase (TS) expression in tumour cells, leading to synergy between irinotecan and 5-FU that is maximal when irinotecan is given 24 h prior to 5-FU. Given this observed synergy and the confirmatory clinical activity of combination therapy with 5-FU, leucovorin (LV) and irinotecan, we performed a phase I trial to determine the maximum tolerated doses (MTD) of UFT, LV, and irinotecan. Treatment consisted of irinotecan administered as a 90-min intravenous (i.v.) infusion on day 1 followed by twice daily oral UFT/LV on days 2–15, repeated every 21 days. Initial doses were irinotecan 200 mg/m^2 and UFT 200 mg/m^2/day, with LV dose fixed at 60 mg/day. 31 patients received a total of 130 cycles of UFT/LV and irinotecan. 3 of 9 patients experienced grade 3/4 diarrhoea at the highest dose level of irinotecan 310 mg/m^2 and UFT 300 mg/m^2/day. Other toxicities included neutropenia, anaemia, alopecia, nausea/vomiting and fatigue. Further dose escalation was not pursued since this level of toxicity was appropriate for future phase II study. One patient with colorectal cancer experienced a partial response and 9 patients with non-small cell lung, colorectal and gastro-oesophageal junction carcinomas had disease stabilisation lasting 4–26 (median 6) cycles. Methylenetetrahydrofolate reductase (MTHFR) C677T genotype was analysed in peripheral mononuclear cells (PMNs) obtained from 24 patients. 2 patients had the homozygous TT polymorphism and 1 of them had grade 3 diarrhoea at the first dose level. Irinotecan on day 1 followed by a 14-day course of oral UFT/LV beginning on day 2 is well tolerated, and suitable for testing in several tumour types. Doses recommended for further study on this schedule are irinotecan 310 mg/m^2 and UFT 300 mg/m^2/day, with LV 60 mg/day.

Keywords: UFT; Irinotecan; Colorectal cancer; Non-small cell lung cancer; MTHFR

1. Introduction

Fluoropyrimidines remain the mainstay of treatment for colorectal cancer, and oral preparations are being explored in combination. UFT (BMS-200604, Uftoral®) is an oral fluoropyrimidine that combines uracil and the 5-fluorouracil (5-FU) prodrug ftorafur in a 4:1 molar ratio [1]. Ftorafur (1-(2-tetrahydrofuranyl)-5-fluorouracil) is generally 100% absorbed after oral administration and is converted to 5-FU by two mechanisms; cytochrome P450 oxidation at C-5′ to yield succinaldehyde and 5-FU, and soluble enzyme hydrolysis at C-2′ to yield 5-FU and 4-hydroxybutanal [1,2]. Uracil, an endogenous dihydropyrimidine dehydrogenase (DPD) substrate, potentiates 5-FU by inhibiting its eventual catabolism to α-fluoro-β-alanine by DPD *in vitro* and *in vivo*, resulting in a higher intratumoural concentration of 5-FU [3]. Phase II studies of single-agent UFT from Japan reported activity in a variety of tumours, with response rates of 25% in gastrointestinal malignancies and 32% in breast cancer [4]. In an attempt to improve the efficacy of UFT, studies were conducted with the combination of UFT and

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leucovorin (LV), to increase the availability of reduced folates and stabilise the binding of 5-fluorodeoxyuridine monophosphate (5-FdUMP) to thymidylate synthase (TS) [5,6]. Phase I combination studies of UFT with LV have led to a 28-day schedule of UFT 350 mg/m^2/day and LV 150 mg/day as the recommended dose for phase II studies [7,8]. Diarrhoea, nausea and vomiting were dose-limiting. Phase II combination trials with LV (75 mg/day) showed response rates of approximately 40% in untreated patients with advanced colorectal carcinoma [9–11]. Grade 3-4 diarrhoea prompted UFT dose reduction to 300 mg/m^2/day in one study, while UFT doses of 350–390 mg/m^2/day were tolerated in the other trials.

Irinotecan is a potent inhibitor of topoisomerase I, a nuclear enzyme that plays a critical role in DNA replication and transcription. Irinotecan binds to the topoisomerase I–DNA complex and inhibits reannealing of the DNA; a subsequent encounter with a replication fork creates a double-strand break, ultimately leading to cell death [12]. Irinotecan has demonstrated antitumour activity against metastatic colorectal cancer as single agent in both chemotherapy-naïve and 5-FU-refractory patients [13–15]. *In vitro* studies have shown that irinotecan downregulates TS expression in tumour cells, leading to synergy between irinotecan and 5-FU that is maximal when irinotecan is applied 24 h prior to 5-FU [16–18]. This observation suggests that the interaction between 5-FU and irinotecan may be critically dependent on the administration schedule. The superiority of the combination 5-FU/irinotecan has been confirmed in numerous clinical trials including two phase III studies which demonstrated a significantly prolonged progression-free survival and overall survival in the irinotecan/5-FU/LV group compared with the 5-FU/LV group [19,20]. However, the incidence of severe diarrhoea was higher in patients treated with both irinotecan and 5-FU.

Phase I irinotecan studies conducted in Europe recommended a single intravenous (i.v.) dose of 350 mg/m^2, every 3 weeks [21,22]. Neutropenia and gastrointestinal toxicity were dose-limiting, with grade 3/4 neutropenia developing in 47% of patients and diarrhoea in 39% of patients in subsequent phase II studies [21]. A phase I trial in colorectal cancer using this regimen, yielded a response rate of 18% in both the previously untreated group and in 5-FU failures [22]. When three different irinotecan administration schedules were evaluated in a European phase I study, the every-3-week dosing emerged as the one allowing the highest dose intensity and the best tolerability profile compared with the weekly regimen [23].

Several determinants of fluoropyrimidines action are known, including expression of the target enzyme TS, of associated enzymes DPD and thymidine phosphorylase, and polymorphisms in the regulatory regions of TS [24]. Studies with folinic acid have demonstrated the dependence of 5-FU toxicity on intracellular levels of reduced folate [25,26]. A polymorphism in a methylenetetrahydrofolate reductase (MTHFR) results in an increase in intracellular reduced folate pools, and may therefore be expected to yield higher 5-FU toxicity [27]. We determined the genotype of patients in this study at the relevant MTHFR locus, to determine if an association could be detected with UFT toxicity.

Given the *in vitro* synergy between irinotecan and 5-FU and the confirmatory clinical activity of combination therapy with 5-FU, LV and irinotecan [19,20], we performed a phase I trial to determine the MTD of UFT, LV, and irinotecan when administered to patients with advanced malignancies. Based on the *in vitro* observation that the synergy between 5-FU and irinotecan may be critically dependent on the schedule, we chose to administer irinotecan on day one, followed by a 14-day course of oral UFT/LV beginning on day 2. The resulting regimen permitted the administration of both drugs at doses close to their single agent phase II doses with tolerable toxicity.

2. Patients and methods

2.1. Eligibility

Eligible patients were at least 18 years of age with histologically-confirmed solid tumours that were refractory to standard therapy or for which no effective therapy was available. An Eastern Cooperative Oncology Group (ECOG) performance status $\leqslant 2$ and a life expectancy $\geqslant 3$ months were required. Patients had adequate bone marrow (neutrophils $\geqslant 1.5\times10^9$ cells/l and platelets $\geqslant 100\times10^9$ cells/l), kidney (serum creatinine $\leqslant 176.8$ μmol/l), and hepatic (serum bilirubin $\leqslant 25.65$ μmol/l, and aspartale aminotransferase/alanine aminotransferase (AST/ALT) $\leqslant 2.5$ times the upper limit of normal) function. All patients had recovered from prior treatment and had received no cytotoxic chemotherapy in the previous 3 weeks (6 weeks for nitrosoureas and mitomycin C). All patients received information on the purpose and conduct of this study, and signed a written informed consent form.

2.2. Pretreatment evaluation and follow-up

Pretreatment evaluation consisted of a history and physical examination, full blood count, serum electrolytes, creatinine and liver function tests, urinalysis, electrocardiogram, baseline imaging study, and assessment of ECOG performance status. Blood counts were performed weekly, biochemical profiles including liver function tests every 3 weeks, and patients were examined prior to every course. Toxicity during each treatment cycle was assigned according to the National Cancer Institute (NCI) Common Toxicity Criteria,

Version 2.0 (Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD, USA). Doses were not modified for nausea, vomiting, alopecia or anaemia. Doses were not escalated for individual patients. Lesions noted at baseline that were measured or evaluated by radiographical scan or X-ray were reviewed before each alternate course and evaluated for response according to standard criteria [28]. Patients exhibiting response to the treatment or stable disease continued on therapy until progression.

2.3. Drug administration

UFT was supplied by Bristol-Myers Squibb Pharmaceuticals (Wallingford, CT, USA) as opaque, white capsules each containing 100 mg of ftorafur and 224 mg of uracil. UFT was administered orally in two divided doses (every 12 h) at a total daily dose as outlined below, on days 2–15 of each 21-day treatment cycle, 1 h prior or following a meal. Irinotecan is formulated in 2-ml vials containing 40 mg of drug and 5-ml vials containing 100 mg of drug. Irinotecan was reconstituted in 250 ml of 5% dextrose in water (D5W) and was administered over 90 min on day 1 of each 21-day treatment cycle with dose escalation as below. Leucovorin was in scored tablets containing 15 mg leucovorin as the calcium salt. LV was administered at 60 mg/day (flat dosing) at all dose levels of irinotecan and UFT. Two 15-mg tablets were administered orally with each dose of UFT on days 2–15 of each treatment cycle. All patients received prophylactic antiemetic premedication with 5HT3 antagonists prior to each dose of irinotecan. Use of granulocyte-colony stimulating factor (G-CSF) or granulocyte-monocyte-colony stimulating factor (GM-CSF) was not permitted during the study.

2.4. Study design

The purpose of this trial was to determine the safety and tolerability of the combination of UFT and irinotecan with a fixed dose of leucovorin. The starting doses were irinotecan 200 mg/m^2 on day 1 and UFT 200 mg/m^2/day on days 2–15, respectively. The dose escalation strategy is presented in Table 1. One cycle of irinotecan and UFT/LV was administered every 21 days. The dose of LV remained fixed at 60 mg/day at all dose levels of UFT and irinotecan. There was no dose escalation of the chemotherapy in individual patients. Patients were requested to document UFT dosing with standardised log sheets and were instructed to notify the research staff if a dose was omitted and to not make up missed doses. The dose-limiting toxicity (DLT) was defined as (1) absolute neutrophil count $<0.5\times10^9$ cells/l for 5 days or platelet count $<25\times10^9$ cells/l, (2) diarrhoea $\geqslant$Common Toxicity Criteria (CTC) grade 3 despite loperamide support, (3) other non-haematological toxicity $\geqslant$grade 3, or (4) receipt of $<75\%$ of planned dose of both drugs in a cycle. Nausea and vomiting were not considered DLTs unless maximally treated with antiemetics. If DLT was observed in any patient, an additional 3 patients were treated at that dose level. In the absence of DLT, escalation proceeded to the next dose level. The maximum tolerated dose (MTD) was defined as one dose level below the dose that induced DLT in greater than one-third of patients.

Table 1
Dose Escalation strategy

Dose level	Irinotecan (mg/m^2)	UFT (mg/m^2)	Leucovorin (mg/day)
1	200	200	60
2	250	200	60
3	250	250	60
4	310	250	60
5	310	300	60

2.5. Genotyping for MTHFR

Peripheral blood mononuclear cells (PMNs) from 24 patients were isolated before treatment using Vacutainer CPT cell preparation tubes (Becton Dickinson and Co, Franklin Lakes, NJ, USA). DNA from PMNs was extracted as described by Miller and colleagues in Ref. [29]. MTHFR C677T genotyping was performed with extracted DNA by a multiplex heteroduplexing method as described by Barbaux and colleagues in Ref. [30].

3. Results

3.1. Patient characteristics

A total of 31 patients (15 females and 16 males) with a range of solid tumour diagnoses and good performance status received a total of 130 cycles (range 1–26) of UFT/LV and irinotecan at the five dose levels. 27 patients were evaluable for response and thirty for toxicity. The demographic characteristics of the patients are presented in Table 2.

3.2. Haematological toxicity

Haematological toxicity was generally mild at all dose levels (Table 3). 2 of 10 patients treated with the first dose level developed grade 3-4 neutropenia, which was not dose-limiting and not cumulative, and two grade 3 thrombocytopenia. One patient treated with UFT 200 mg/day and irinotecan 250 mg/m^2 developed grade 3 neutropenia. There was no haematological toxicity at the dose levels 3 and 4. One patient experienced grade 3

neutropenia at dose level 5. There were no episodes of neutropenic fever.

3.3. Non-haematological toxicity

Non-haematological toxicities included diarrhoea, mucositis, nausea/vomiting, alopecia and fatigue (Table 4). Dose-limiting diarrhoea and mucositis were found at the first dose level, at which 2 patients experienced grade 3 diarrhoea and 1 patient grade 4 mucositis. With expanded accrual, no more cases occurred. At the second dose level, 1 patient developed grade 3 diarrhoea. Only grade 1 or 2 diarrhoea was noted at dose levels 3 and 4. 3 out of 9 patients experienced grade 3-4 diarrhoea at the final dose level of irinotecan 310 mg/m^2 and UFT 300 mg/m^2/day. Expansion to 9 patients at this level was based upon the occurrence of DLT's. The 33% rate of severe diarrhoea was consistent with previous studies of irinotecan with i.v. 5-FU [19,20], and so judged reasonable for further phase II study.

Table 2
Patients' characteristics

No. of patients	
Entered	31
Assessable	30
Gender	
Male	16
Female	15
Age (years)	
Median (Range)	54 (28–76)
ECOG Performance Status	
0	13
1	18
Tumour type	
Oesophagus	1
GE junction	1
Colon	10
Rectum	2
Pancreas	1
Cholangiocarcinoma	1
Lung	15
Prior therapy	
Chemotherapy	19
Radiotherapy	0
Chemotherapy and radiotherapy	9
None	3

ECOG, Eastern Cooperative Oncology Group; GE, gastro-oesophageal.

Table 3
Cycle 1 Grade 3/4 haematological toxicity by dose level

Dose Irinotecan/UFT (mg/m^2)	*N*	Neutropenia	Thrombocytopenia	Anaemia
200/200	10	2	2	2
250/200	6	1	0	2
250/250	3	0	0	0
310/250	3	0	0	0
310/300	9	1	0	0

3.4. Response

Antitumour activity was observed with the combination UFT/LV and irinotecan in 10 of 27 of the evaluable patients. 13 of these evaluable patients completed two cycles of treatment and 10 patients received more than four cycles of treatment.

At the first dose level, 1 patient with metastatic colorectal cancer achieved a partial response lasting for four cycles. This patient was a 33-year-old woman with recurrent colon cancer less than 1 year after sigmoid-colon resection followed by adjuvant chemotherapy with 5-FU for a T3N2 colon cancer. She had received no chemotherapy for advanced disease. She had a partial response in the retrocrural and retroperitoneal lymph nodes after two cycles of therapy and a decrease in carcinoembryonic antigen (CEA) from 37.8 to 18.8 ng/ml.

9 patients with non-small cell lung, colorectal, and gastro-esophageal junction carcinomas had disease stabilisation lasting 4–26 (median 6) cycles. At dose level 5, 4 patients with non-small cell lung, gastroesophageal junction and colorectal cancers experienced stable disease for 5–26 cycles. One of these was a 58-year-old woman with non-small cell lung cancer with lung, liver and bone metastases who had failed carboplatin/paclitaxel, gemcitabine and navelbine and had stable disease for 19 cycles. Another was a 40-year-old male with adenocarcinoma of the lung with bone, brain and lymph node metastasis who failed previous carboplatin, paclitaxel and gemcitabine and had stable disease that persisted for 26 cycles.

3.5. MTHFR genotype

MTHFR C677T genotype was analysed in PMNs from 24 patients. 2 of these patients had the homozygous

Table 4
Cycle 1 Grade 3/4 non-haematological toxicity by dose level

Dose Irinotecan/UFT (mg/m^2)	*N*	Diarrhoea	Fatigue	N/V	↑Bilirubin
200/200	10	2[a]	0	4	1
250/200	6	1	0	2	0
250/250	3	0	0	0	0
310/250	3	0	0	0	0
310/300	9	3[a]	0	2	1

N/V, nausea/vomiting.
[a] Dose-limiting toxicity (DLT).

TT polymorphism that results in elevated steady-state reduced folate levels. One of the 2 had grade 3 diarrhoea at the first dose level. Among the 22 patients with the phenotypically normal CC or CT genotypes, there were five episodes of grade 3 or 4 diarrhoea, most of them at the highest dose level.

4. Discussion

Studies conducted in Japan, and subsequently confirmed in Europe, have shown that UFT at doses of 300–400 mg/m^2/day is both well tolerated and has antitumour activity in a variety of solid tumours [4,7,31]. Because LV is known to modulate the activity of 5-FU, the combination of UFT and LV with different administration doses has been investigated and demonstrated a higher efficacy than UFT alone [5,6]. Two phase III studies in patients with untreated metastatic colorectal cancer compared UFT/LV with i.v. bolus 5-FU/LV [32,33]. The two regimens produced similar times to progression, survival and overall responses; however, diarrhoea, mucositis and myelosuppression were significantly less frequent in the UFT/LV arm in both studies. In spite of the results of these studies, the combination of UFT/LV was not approved for use in the United States because of a failure to demonstrate the equivalence of the oral drug, and the availability of an alternative, capecitabine. Strictly speaking, these trials were not powered for equivalence, but the results are consistent with results using other oral fluoropyrimidines [34,35], and for combination trials there is an emerging consensus that oral fluoropyrimidines are an adequate means of 5-FU administration.

Clinical trials of combination of 5-FU and irinotecan have shown superior activity to either irinotecan or fluorouracil alone as front-line therapy for metastatic colorectal cancer [19,20,36]. However, the combination with bolus 5-FU has significant toxicity [37] and attention has been directed to the schedule of 5-FU, and the optimal sequence and interval of administration to overcome the overlapping toxicities. Both the Douillard and Kohne trials used infusional 5-FU, and both showed approximately one-half the risk of grade 3 or 4 diarrhoea as the original Saltz regimen. Oral regimens have the potential to mimic infusions and thus to circumvent the diarrhoea risk. Efforts have been made to combine irinotecan and oxaliplatin with oral fluoropyrimidines, to avoid the complexities of infusional therapy [38,39]. In particular, the combination irinotecan/capecitabine in patients with advanced colorectal cancer has shown substantial activity across doses and manageable toxicity. Response rates range from 38 to 65% [40,41]. These results support the further use of the combination of UFT with irinotecan as described in this study.

Experimental evidence has produced conflicting results concerning the interaction between TS and topoisomerase I inhibitors [17,42–44]. This has been reflected in the clinic, in which the evidence for an effect greater that a simple additive–response profile has not been manifest in colorectal cancer. One focus has been on the most appropriate sequence of administration and the interval between drug administration. Most studies have shown a better therapeutic interaction when irinotecan is administered 24 h prior to 5-FU [16–18]. Therefore, in this study, we chose to administer irinotecan on day 1, followed by a 14-day course of oral UFT/LV beginning on day 2. We found this combination to be well tolerated when administered on this schedule in refractory solid tumours. We were able to administer UFT and irinotecan at doses similar to the single-agent standard doses with mild toxicity, and irinotecan 310 mg/m^2 and UFT 300 mg/m^2/day were the recommended doses for further study. Not surprisingly, the DLT was diarrhoea, which occurred at a rate of 33% at the recommended phase II dose. We did not pursue further dose escalation because this rate of toxicity is acceptable for further development. Toxicity was not cumulative, and did not prevent prolonged administration of this regimen to patients exhibiting clinical benefit. 7 patients received more than six cycles including 2 patients with NSCLC who were treated for 19 and 26 cycles. This level of clinical benefit is at least promising in this refractory patient population, although no evidence to support the contribution of the sequential schedule to that activity can be adduced.

A phase I trial of irinotecan and UFT as second-line treatment for advanced colorectal cancer was recently conducted in Spain with a different administration schedule [45]. The recommended doses for phase II studies were irinotecan 110 mg/m^2 on days 1, 8 and 15 every 28 days and UFT 250 mg/m^2 on days 1–21 or irinotecan 100 mg/m^2 and UFT 300 mg/m^2. These doses are almost identical to those reached in the current study. The toxicity profile was similar with diarrhoea being observed in 32% of patients. Similar results were also shown in a phase I/II study of irinotecan on day 1 and UFT/LV on days 1–14 every 21 days with seven of 25 patients achieving complete or partial responses and 11 patients stable disease [46]. The recommended doses for further studies were irinotecan 250 mg/m^2 and UFT 300 mg/m^2 and LV 45 mg/day. Therefore, our findings are consistent with those of others with this combination.

Although at the time our study was conducted there were no formal comparison between the weekly and every-three week irinotecan schedules, separate clinical trials indicated equivalent efficacy. However, the toxicity profile seemed more favourable with the 3-week schedule [23]. Furthermore, the 3-week schedule was chosen in two phase III studies demonstrating a significant survival improvement in patients receiving

irinotecan compared with patients receiving either supportive care or infusional 5-FU [14,15]. Based on the similar efficacy of the two irinotecan schedules, the more favourable toxicity of the 3-week regimen and the convenience for the outpatient setting, we chose to investigate the every-3-week irinotecan dosing. A recent phase III trial comparing the efficacy and tolerability of the weekly and 3-week schedules in patients with 5-FU-refractory metastatic colorectal cancer confirmed similar efficacy and quality of life. However, a higher incidence of severe diarrhoea was associated with the weekly regimen [47]. These findings support the further development of the regimen described here.

In this phase I trial, we attempted to discern if there was a significant effect of MTHFR polymorphism on the incidence or severity of diarrhoea. The interpretation of the clinical data is complicated by the fact that both irinotecan and 5-FU are dose-limited by this toxicity, but we had previously demonstrated a relationship in a study of raltitrexed and irinotecan [48]. Further, only two of the subjects with samples that could be analysed had the TT genotype. Even so, one of these had toxicity at the first dose level, and continued analysis of patients to determine the relevance of this potential marker should be undertaken.

Although evaluation of the response rate was not the main objective of this study, we observed evidence for clinical activity in several diseases, and periods of prolonged stable disease were observed in 2 patients with non-small cell lung cancer. 5-FU as a single agent has minimal activity in lung cancer, however, *in vitro* data suggests synergism when combined with other agents [49]. *In vitro* and *in vivo* data have established the activity of irinotecan in lung cancer both as a single agent, with response rates ranging from 11 to 34%, and in combination with other chemotherapeutic agents including cisplatin, gemcitabine and taxanes [50]. Regimens of non-platinum-containing combinations have shown that efficacy is equivalent to that obtained with platinum-based combinations with a median survival time ranging from 7 to 9 months, and 1-year survival from 30% to 40%, making the toxicity profile a critical determinant in the selection of the regimen [51]. One phase I trial of UFT and irinotecan was conducted in Japan in patients with lung cancer [52]. UFT was administered at 400 mg twice daily for 7 days followed by irinotecan as a continuous infusion over 24 h on day 8. Irinotecan 140 mg/m^2 and UFT 400 mg twice daily were the recommended doses for further study. 3 of 4 patients experienced grade 3 or 4 diarrhoea and/or leucopenia. 5 of 12 evaluable patients achieved partial response. Further studies of this combination in patients with gastro-oesophageal, colorectal and lung cancers are warranted, as an alternative to combinations of irinotecan with bolus or infusional 5-FU, capecitabine and other oral fluoropyrimidines.

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