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Randomised study of tegafur and oral leucovorin *versus* intravenous 5-fluorouracil and leucovorin in patients with advanced colorectal cancer

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Abstract

This randomised, open-label trial compared oral tegafur (FT)/leucovorin (LV) with the intravenous bolus 5-fluorouracil (5-FU)/LV as first-line chemotherapy for advanced colorectal cancer (CRC). Patients were randomised to receive oral FT 750 mg/m^2/day for 21 days and LV 15 mg/m^2 every 8 h in cycles repeated every 28 days ($n = 114$), or intravenous LV 20 mg/m^2 followed by 5-FU 425 mg/m^2 daily for 5 days every 4 weeks for 2 cycles, and later every 5 weeks ($n = 123$). Response rate was significantly higher in the FT/LV arm (27%, 95% CI 19–35) than in the 5-FU/LV arm (13%, 95% CI 7–19) ($p < 0.004$). The median time to progression was 5.9 months (95% CI, 5.3–6.5; FT/LV arm) and 6.2 months (95% CI, 5.4–6.9; 5-FU/LV arm). Median overall survival was 12.4 months (95% CI, 10.3–14.5 months; FT/LV arm) and 12.2 months (95% CI, 8.9–15.7 months; 5-FU/LV arm) (p = n.s.; hazard ratio FT/LV:5-FU/LV = 1.02). 5-FU/LV showed a higher incidence of grade 3/4 neutropenia (4.1 *vs.* 0%). Non-hematological toxicities showed similar incidences in the two treatment arms. Oral FT/LV was more active than IV 5-FU/LV in terms of objective response rate with similar overall survival, and with a favorable toxicity profile. This makes FT/LV a valid alternative to the IV 5-FU schedule in CRC patients.

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1. Introduction

Chemotherapy with intravenous (i.v.) 5-fluorouracil (5-FU) and leucovorin (LV) has been widely used for treatment of advanced colorectal cancer (CRC) [1–3] and was the backbone of treatment until the introduction of novel chemotherapy agents such as irinotecan or oxaliplatin and their combinations with 5-FU/LV. Nevertheless, research is still advancing on the development of orally administered 5-FU prodrugs that might offer an equivalent efficacy or improve tolerability compared to i.v. 5-FU, but also a more convenient form of administration [4]. Such a 5-FU prodrug might be modulated with LV and combined with new chemotherapeutic agents.

Tegafur (FT) is a 5-FU prodrug that has almost complete oral bioavailability and is converted by cytochrome P_{450} hepatic isoenzymes to 5-FU [5]. Controlled studies in patients with advanced CRC showed a similar antitumoral efficacy of FT 1 g/m^2/day for 21 days than IV 5-FU [6–8]. Biochemical modulation of FT with oral LV constitutes a treatment pharmacokinetically similar to a continuous infusion of 5-FU plus LV, but with the significant advantage of an oral, outpatient administration [9]. An initial dose-finding study recommended FT 750 mg/m^2/day for 21 days with continuous oral LV 45 mg/day in a 28-day cycle [10]. A further phase II study showed an overall response rate of 38% and tumour control in 69% of patients that lasted for more than 7 months [9]. The non-hematologic toxicity profile was similar to bolus 5-FU/LV, with negligible hematological toxicity. Recuperation from toxicity was rapid and managed primarily on an outpatient basis.

In view of the significant response rate and favorable safety profile found in this phase II study, this multicenter, randomised, open-label study was designed to compare the efficacy and safety of an oral regimen of FT and LV to the i.v. Mayo Clinic regimen of bolus 5-FU and LV in patients with previously untreated advanced CRC. This was an equivalence trial, as the hypothesis tested was that FT/LV regimen might have a similar antitumoral efficacy than i.v. 5-FU/LV.

2. Patients and methods

2.1. Study design

This was a randomised, multicenter, open-label clinical trial comparing oral FT/LV to i.v. 5-FU/LV as first-line chemotherapy of patients with advanced CRC. The study (TEGAFUR/97/V1) was conducted in 16 Spanish hospitals following the Declaration of Helsinki, the Good Clinical Practice guidelines, and current Spanish regulations on clinical trials. All patients provided their informed consent, and the Ethics Committees of all participating centers approved the study prior to any study procedure.

2.2. Patient selection

Eligible patients were required to be $\geqslant$18 years old and show a histologically confirmed diagnosis of advanced or metastatic CRC with bidimensionally measurable disease, a Karnofsky performance status $\geqslant$60, and a life expectancy >3 months. Locally advanced disease had to be not amenable to curative surgery. Adequate bone marrow (absolute granulocyte count $\geqslant$1500/mm^3 and platelet count $\geqslant$100 000/mm^3), liver (bilirubin within the institution's upper limit of normal) and renal (creatinine within the institution's upper limit of normal) function was also required.

Patients were excluded if they had received previous chemotherapy (except for adjuvant chemotherapy at least 6 months before inclusion) or if they showed serious uncontrolled, concurrent medical condition (infection, unstable cardiopathy or cardiovascular disease requiring treatment, or chronic diarrhea). Patients with previous cancer history (except for resolved cervical carcinoma or basal cutaneous carcinoma) were excluded. Previous (at least one month before inclusion) non-extensive radiotherapy was allowed in non-evaluable sites. Lactating/pregnant women or patients with reproductive potential required to implement adequate contraceptive measures.

2.3. Treatment

Patients were contacted by telephone from the study coordinating center and were centrally randomised to treatment with either oral FT/LV or i.v. 5-FU/LV. Patients were randomly assigned in blocks of 4 and stratified by center in order to guarantee a homogeneous number of patients in each study arm at each participating center.

In the FT/LV treatment arm, tegafur 750 mg/m^2/day was administered in two or three oral doses (depending on the total dose) after meals for 21 consecutive days in 28-day cycles. Each capsules contained 400 mg of tegafur; hence, daily doses were rounded to the nearest multiple according to body surface area. LV was administered continuously (15 mg orally every 8 h). In the 5-FU/LV treatment arm, LV 20 mg/m^2 followed by 5-FU 425 mg/m^2 were administered as i.v. bolus for 5 consecutive days with cycles repeated every 28 days during 2 cycles and later every 35 days.

Patients experiencing toxicities ⩽grade 2 received symptomatic treatment and no dose reduction in further cycles. In patients developing severe toxicity (*i.e.*, granulocyte count 1000–1500/mm^3 or platelet count 75 000–100 000/mm^3 or non-hematological toxicity ⩾grade 3), treatment was suspended until complete resolution of symptoms and was then continued with a 25% dose reduction in subsequent cycles. After dose reduction, no dose re-escalation was allowed. Patients were withdrawn from the study if they showed granulocyte count <1000/mm^3 or platelet count <75 000/mm^3 or non-hematological toxicity grade 4 after the first dose reduction. Patients were also withdrawn in the event of dose delay >3 weeks. Delay and subsequent 25% dose reduction were allowed if grade 2 non-hematological toxicity appeared early in the FT/LV arm. Treatment was maintained until disease progression, unacceptable toxicity or consent withdrawal.

2.4. Assessment of response and toxicity

The baseline evaluation included medical history, physical examination, ECG, complete differential blood count, serum biochemistry, and assessment of tumour dimensions with chest-X-ray or computer tomography scans. Before each cycle, adverse events were documented and a physical examination, differential blood count and blood biochemistry test were performed. Other tests were carried out as determined by the clinical manifestations.

All patients receiving at least one chemotherapy cycle were considered to be evaluable for antitumoral efficacy and toxicity. Response to treatment was classified according to WHO criteria [11]. Tumour response rates (including 95% CIs) were calculated as the proportion of patients who experienced a complete or partial response. Patients not evaluable for responses were classified according with the possible worst condition (*i.e.*, progressive disease). Chi-squared test was used to detect differences in response rate between the treatment arms. Overall survival was calculated from randomisation to the date of death due to any cause. Time to disease progression (TTP) was calculated from randomisation to the first documentation of disease progression. All toxicities experienced during the study were recorded and graded according to the National Cancer Institute's (NCI) common toxicity criteria [12]. All patients were evaluated for adverse events regardless of their relationship to the study drug. All adverse events were graded for severity before each treatment cycle.

2.5. Statistical analysis

The primary endpoint of this study was the objective response rate (ORR), and the study was designed to demonstrate that FT/LV was at least as effective as 5-FU/LV in terms of ORR. Initial sample size calculations required 148 patients in each treatment arm (total of 296 patients) to ensure 80% power (one-sided $\alpha = 0.05$, withdrawal rate = 10%) to demonstrate an equivalence in the objective response rate. We assumed a 23% response rate in the 5-FU/LV arm, and a margin of equivalence of 15% in the objective response rate.

Statistical analyses were performed using the SPSS v.10 statistical package. Toxicity analyses were performed on patients who received at least one dose of study treatment (safety population). All efficacy analyses were conducted on the intent-to-treat (ITT) population. Kaplan–Meier estimations were used for overall survival and time to progression. The adverse events and response were calculated by punctual estimation with a 95% confidence interval (95% CI).

3. Results

3.1. Patient characteristics

Patients were enrolled between September 1997 and December 2000 when, due to the slow enrolment rate, the investigator team decided to finish recruitment with 246 randomised patients (85% of the expected total sample size). In October 2000, a preliminary analysis of data from 198 patients was done. This preliminary analysis showed no therapeutic inferiority of FT/LV *vs.* 5-FU/LV: response was 11% higher with FT/LV in absolute terms, and 50% higher in relative terms (RR = 1.51). The RR confidence interval (unilateral contrast at 97.5%) was [−0.03 to 0.25]. FT/LV was evaluated as equally efficacious as 5-FU/LV; in the worst case, response with FT/LV could be only a 3% lower and, accordingly, enrolment was stopped two months later.

Nine enrolled patients were not included in the study due to protocol violation or unavailable information previous to randomisation (Fig. 1). The treatment arms were well balanced with respect to demographic and baseline disease characteristics (Table 1). Widespread involvement with distant disease sites was reported in 94–96% of patients.

Only 19–20% and 11% of patients had received prior adjuvant 5-FU based chemotherapy and radiotherapy, respectively. Most patients (86–90%) had previously undergone surgery. This surgery was radical in 47–53% of cases. Twenty-three (20%) and 12 (10%) patients underwent a second surgical procedure in the FT/LV and 5-FU/LV treatment arms, respectively. Overall, 94 of 237 treated patients continued receiving treatment after the end of the study with second-line agents. In the FT/LV treatment arm, 48 patients were mainly treated with irinotecan and combination of oxaliplatin + irinotecan in 27% and 20% of cases, respectively. Likewise, in the 5-FU/LV treatment arm, 46 patients involved in

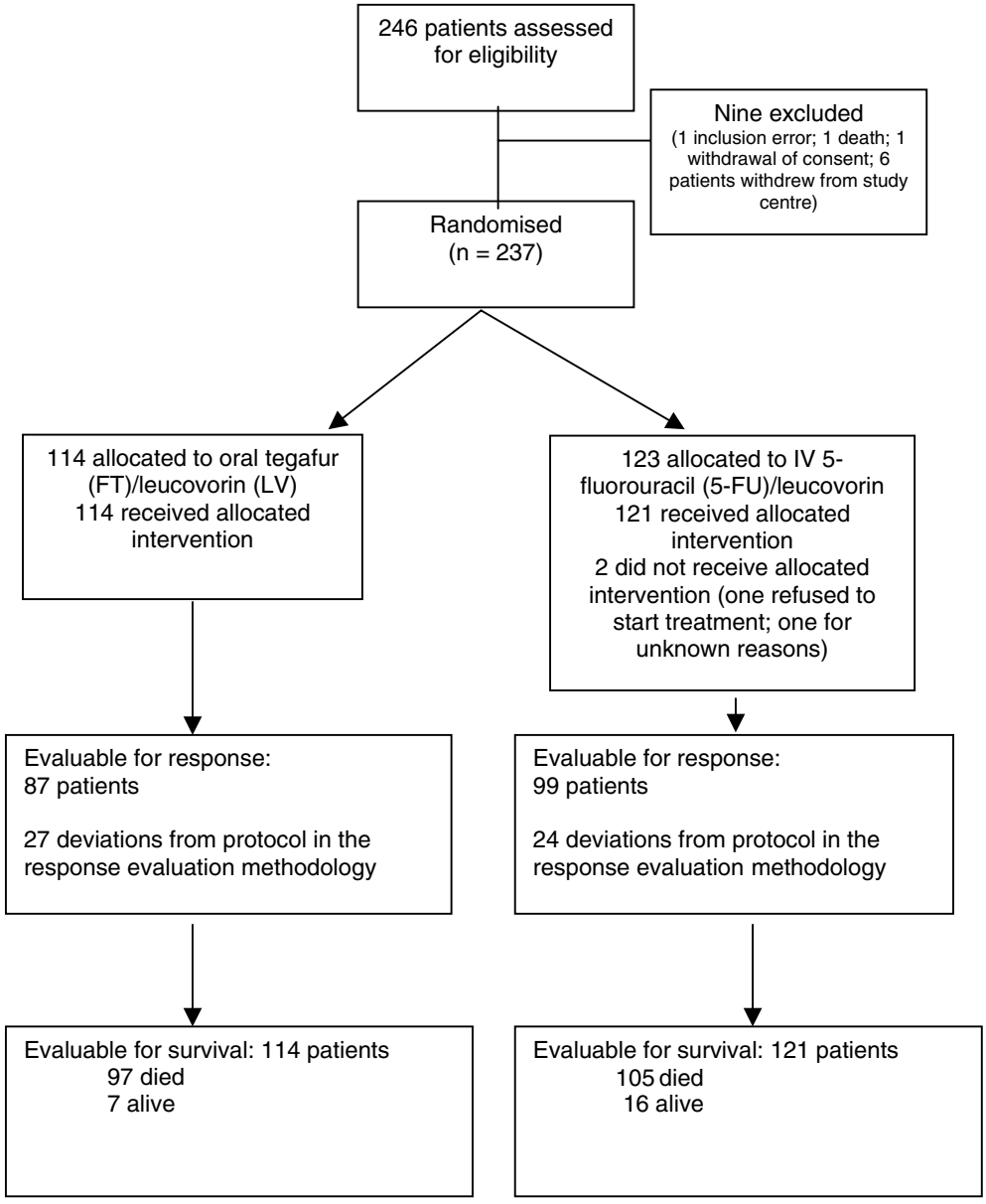

Fig. 1. Flowchart of patients' progress through the trial.

second-line therapy received irinotecan and combination of oxaliplatin + irinotecan in 30.5% and 28.3% of cases, respectively.

3.2. Treatment

Of the 237 treated patients, two patients in the 5-FU/LV-treatment arm did not complete the first cycle of treatment. In the remaining 235 patients, a total of 671 cycles (median per patient = 5; range 1–24) and 633 cycles (median per patient = 5; range 1–20) were administered during the study in the FT/LV and 5-FU/LV treatment arms, respectively (Table 2). Overall, 55.7% of patients received 1–5 cycles, and 34.2% of patients received 6–10 cycles. Only 9 patients received more than 15 cycles. Treatment was delayed and dose was reduced more frequently ($P < 0.001$) in the FT/LV treatment arm (Table 2).

3.3. Primary efficacy endpoint: antitumoral response

Table 3 shows the best tumour response found during the study. The overall response rate (ORR) was significantly higher in the FT/LV arm (27%, 95% CI 19–35) than in the 5-FU/LV arm (13%, 95% CI 7–19) ($P < 0.004$). This higher ORR in the FT/LC arm was related to a higher number of partial responses (24% *vs.* 10%, respectively). The percentage of patients

Table 1
Patient and disease characteristics at baseline

Characteristic	FT/LV ($n = 114$)	5-FU/LV ($n = 123$)
Age (years)		
Median	67	68
Range	30–82	31–82
Gender		
Male	71 (62%)	83 (68%)
Female	43 (38%)	40 (32%)
Karnofsky performance status[a]		
100	30 (27%)	34 (29%)
80–90	59 (54%)	65 (55%)
60–70	21 (19%)	20 (16%)
Site of primary disease		
Colon	66 (58%)	77 (63%)
Rectum	47 (41%)	44 (35%)
Colorectal	1 (1%)	2 (2%)
Metastatic sites		
No. of sites involved		
1	7 (6%)	5 (4%)
2	73 (64%)	82 (67%)
>3	34 (30%)	36 (29%)
Disease sites[b]		
Liver	77 (67%)	90 (73%)
Lung	38 (33%)	40 (33%)
Lymph nodes	10 (9%)	13 (11%)
Peritoneal	10 (9%)	6 (5%)
Other	17 (11%)	11 (8%)
Prior treatment		
Surgery	102 (90%)	106 (86%)
Radiotherapy	13 (11%)	14 (11%)
Adjuvant chemotherapy	23 (20%)	23 (19%)

5-FU, 5-fluorouracil; LV, leucovorin. Data shown are *n* (%).
[a] Unknown in 8 patients.
[b] The patients could show more than one metastatic site.

Table 2
Treatment administration

Characteristics	FT/LV ($n = 114$)	5-FU/LV ($n = 123$)
Cycles (n)	671	633
Median (range)	5 (1–24)	5 (1–20)
Treatment delay		
Patients	49 (43%)	28 (23%)
Cycles	79 (12%)	34 (5%)
Dose reduction		
Patients	44 (39%)	34 (28%)
Cycles	97 (15%)	74 (12%)

5-FU, 5-fluorouracil; LV, leucovorin. Data shown are *n* (%).

reporting stable disease was similar in both treatment arms (FT/LV, 33%; 5-FU/LV, 32%).

3.4. Survival

A total of 202 deaths (85.2%) were reported in 237 patients, with a similar distribution in both treatment arms: 97 events (85.1%) in the FT/LV arm and 105 events (85.4%) in the 5-FU/LV arm. Deaths were mostly due to progression of the disease (87.6% and 83.8% in FT/LV and 5-FU/LV arms, respectively). Four toxic deaths were reported, two in each treatment arm. Toxic deaths were due to diarrhea ($n = 1$), pneumonia subsequent to neutropenia ($n = 1$), acute abdominal complication ($n = 1$), and unknown case ($n = 1$).

Table 3
Best tumour response and overall response rate (intention-to-treat analysis)

	FT/LV ($n = 114$)	5-FU/LV ($n = 123$)
Complete response	3 (3%)	4 (3%)
Partial response	27 (24%)	12 (10%)
Stable disease	38 (33%)	39 (32%)
Progressive disease	19 (17%)	44 (36%)
Not evaluable[a]	27 (23%)	24 (19%)
ORR	27% (95% CI, 19–35%)	13% (95% CI, 7–19%)
Tumour control rate	60% (95% CI, 51–69%)	45% (95% CI, 36–54%)

Data shown are *n* (%). ORR, overall response rate.
[a] Patients lost to follow-up, who withdrew consent, or who had incomplete measurements.

The median survival time was 12.4 months (95% CI, 10.3–14.5 months) in the FT/LV treatment arm and 12.2 months (95% CI, 8.9–15.7 months) in the 5-FU/LV-treatment arm (Fig. 2). No significant differences between treatment arms were found (hazard ratio FT/LV:5-FU/LV = 1.02).

3.5. Time to disease progression

The median TTP was 5.9 months (95% CI, 5.3–6.5) in the FT/LV treatment arm and 6.2 months (95% CI, 5.4–6.9) in the 5-FU/LV treatment arm (Fig. 3). No significant differences between treatment arms were found.

3.6. Toxicity

Both treatments were well tolerated, and toxicities like nausea/vomiting, stomatitis or skin toxicity were mainly of grade 1/2 (Table 4). Nevertheless, the 5-FU/LV treatment arm showed five cases of grade 3/4 neutropenia (4%), one of these was followed by pneumonia and death, whereas no severe neutropenia was reported in the FV/LV treatment arm. No febrile neutropenia or other hematological toxicities were reported in either treatment arm. The overall distribution of grade 3/4 non-hematological toxicity was similar in the two treatment arms. In both arms, diarrhea, asthenia and stomatitis were the most prevalent toxicity (18%, 11% and 6% in FT/LV *vs.* 14%, 5% and 7% in 5-FU/LV, respectively).

4. Discussion

The main results of this multicenter, randomised, open-label clinical trial confirmed the main hypothesis tested: oral FT/LV regimen was at least as active as

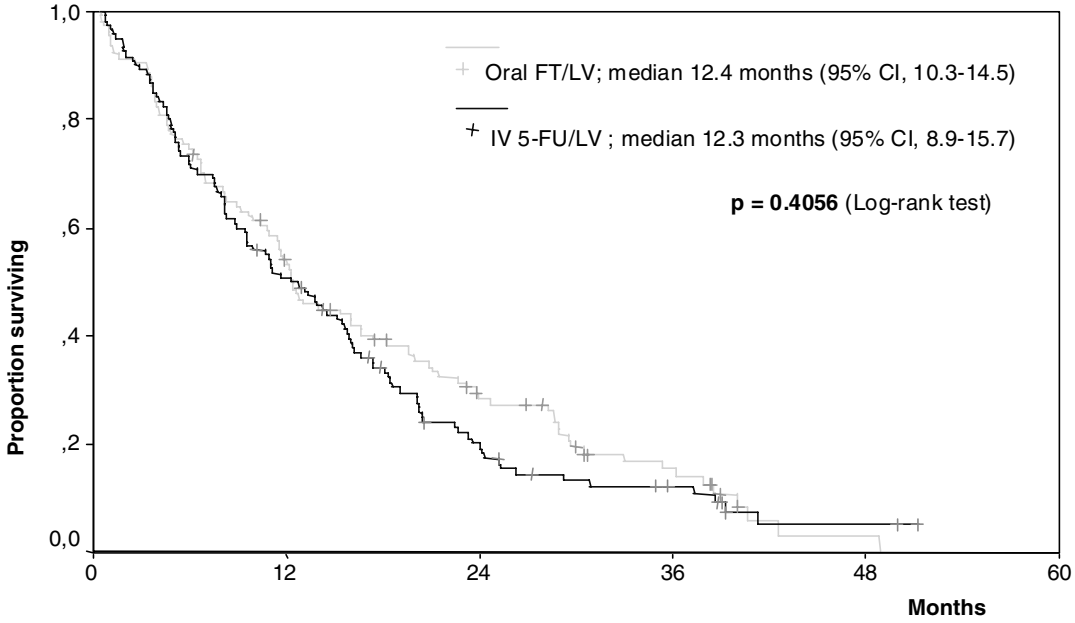

Fig. 2. Overall survival. FT/LV ($n = 114$); 5-FU/LV ($n = 123$). FT, tegafur; LV, leucovorin; 5-FU, 5-fluorouracil.

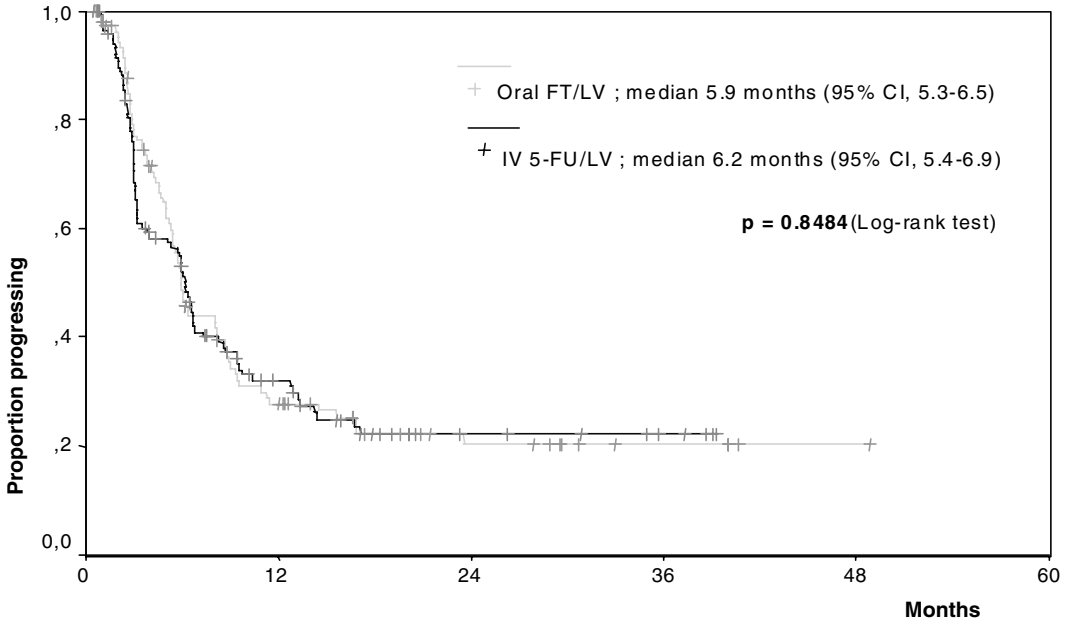

Fig. 3. Time to progression. FT/LV ($n = 114$); 5-FU/LV ($n = 123$). FT, tegafur; LV, leucovorin; 5-FU, 5-fluorouracil.

i.v. bolus 5-FU/LV (Mayo regimen). Although the sample size was lower than that initially estimated, ORR was significantly higher in patients treated with FT/LV (26.2%) than in patients treated with 5-FU/LV (13%). A high ORR (33.3%) was also found in our previous phase II trial evaluating the same FT/LV regimen [9]. As commented in Section 3, a preliminary analysis of data ($n = 198$) done in October 2000 predicted minor changes in response if recruitment was completed in accordance with the initial estimated sample size ($n = 296$). Final data ($n = 246$; including 48 additional patients) showed a RR for response rate of 2.11 (95% CI, 1.23–3.60): the probability for showing an objective response in the FT/LV was 111% higher, and the 95% CI reported confirmed that, in the worst case, response in FT/LV arm should be 23% higher. This difference should be clinically relevant (*i.e.*, >than the margin of equivalence of 15% in the objective response rate considered in the calculation of sample size). Statistical simulations conducted assumed complete enrolment in the

Table 4
Treatment-related toxicities per patient

Toxicity	FT/LV ($n = 114$)		5-FU/LV ($n = 123$)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Hematological toxicity				
Neutropenia	–	–	1 (1%)	5 (4%) $^{p < 0.035}$
Non-hematological toxicity				
Alopecia	–	–	2 (2%)	1 (1%)
Asthenia	21 (18%)	12 (11%)	25 (20%)	6 (5%)
Diarrhea	30 (26%)	21 (18%)	48 (39%)	17 (14%)
Fever	–	–	2 (2%)	–
Infection	3 (3%)	–	1 (1%)	2 (2%)
Nausea/vomiting	48 (42%)	9 (8%)	40 (33%)	4 (3%)
Skin toxicity	11 (10%)	1 (1%)	2 (2%)	–
Stomatitis	38 (33%)	7 (6%)	37 (30%)	9 (7%)

Data shown are *n* (%). FT, tegafur; LV, leucovorin; 5-FU, 5-fluorouracil.

worst comparable condition (*i.e.*, no further responses with FT/LV, but further responses with 5-FU/LV) confirmed that in all cases 95% CI for objective response rate should be compatible with the initial hypothesis of equivalence.

We found a median overall survival of 12.4 months with oral FT/LV which was not significantly different from the 12.2 months found with IV 5-FU/LV. The reported hazard ratio FT/LV:5-FU/LV was 1.02, and supported the conclusion of equivalence in survival.

Six previous phase III trials evaluated schedules with different 5-FU prodrugs: UFT/LV [13,14], eniluracil/5-FU [15–29] and capecitabine [20,26,29]. All these studies used the same 5-FU/LV-reference regimen in patients with advanced disease and with a similar study design. Despite this, it is difficult to establish direct comparison between these previous clinical trials and the present study, even though the results for control 5-FU/LV groups were similar in terms of overall response rate and survival. Thus, the response rate and survival found here for the 5-FU/LV arm (13% and 12.2 months) fell into the range (9–15.5% and 10.3–15.5 months) previously reported in the control arms of these studies. This fact would imply that the series of patients studied would have similar prognostic factors and, therefore, an indirect comparison of results may provide information quite close to reality.

Capecitabine is another oral fluoropyrimidine administered as 5-FU prodrug and compared to 5-FU/LV Mayo regimen as first-line chemotherapy in advanced CRC patients: two randomised phase III trials showed a range of ORR (18.9–24.8) (Table 5) with an upper limit similar to the 26.0 found here and overlapping 95% CIs. Similar (4.3–5.2 months) TTP were reported. Capecitabine has shown an overall survival of 12.5–13.2 months in patients treated with this 5-FU prodrug [20,26,29]. Recent pooled data showed an integrated response rate of 26%, TTP of 4.6 months and median survival of 12.9 months [27]. Once again, these survival values are quite similar to that found in the present study.

Tegafur has also been combined with oral uracil at a fixed molar ratio of 1:4 (UFT). Tegafur is a 5-FU prodrug, while uracil modulates 5-FU catabolism by slowing the rate of 5-FU degradation [15,22]. Two large phase III studies conducted in patients with previously untreated metastatic CRC showed that oral UFT plus LV has similar antitumour efficacy compared to the Mayo regimen in terms of ORR (11–12% *vs.* 9–15%) and TTP 3.4–3.5 months *vs.* 3.3–3.8 months [13,14]. Nevertheless, the survival times found in these phase III trials on UFT/LV (12.2–12.4; Table 5) were similar to that found here with FT/LV.

Eniluracil is an inactivator of dihydropyrimidine dehydrogenase, the principal enzyme in the 5-FU catabolic pathway [23]. Eniluracil has been used with 5-FU in 10:1 ratio by oral route. In several phase III studies, the reported ORR were in the range of 11.6–12.2%, without differences with respect to 5-FU/LV. Similar TTP (4.4–5.0 months *vs.* 5.3–5.6 months) were reported [16].

Despite differences in TTP and ORR between all these studies, the overall survival times found here were in keeping with these large trials and confirm that, in terms of survival, FT/LV regimen constitutes a suitable alternative to i.v. bolus 5-FU/LV but might also be an acceptable alternative to other oral fluoropyrimidines. No survival superiority was found for FT/LV over i.v. bolus 5-FU/LV, but FT/LV showed a safety advantage: severe myelosuppression was practically non-existent compared to 5-FU/LV. The low incidence of neutropenia reported here with FT/LV agrees with the low range reported in previous studies on FT/LV [9], but also on FT [6–8], UFT/LV [13,14] or capecitabine [20,26,29] (Table 5). The minimal myelosuppressive effect found with oral FT is explained by the slow metabolism of FT to 5-FU that simulates slow constant infusion of 5-FU and is less myelosuppressive than 5-FU bolus

Table 5
Results found in phase III studies on several 5-FU prodrugs (capecitabine, eniluracil, UFT and FT) as first-line chemotherapy in advanced, metastatic colorectal cancer *vs.* 5FU/LV (Mayo schedule) as control arm

	Capecitabine		Eniluracil/5-FU		UFT/LV		FT/LV
	Hoff *et al.* [20]	Van Cutsem *et al.* [29]	Van Cutsem *et al.* [28]	Schilsky *et al.* [24]	Douillard *et al.* [14]	Carmichael *et al.* [13]	Present study
n	605	602	531	981	816	380	246
ORR (%)	24.8 *vs.* 15.5 $P < 0.005$	18.9 *vs.* 15	11.6 *vs.* 14.4	12.2 *vs.* 12.7	12 *vs.* 15	11 *vs.* 9	27 *vs.* 13 $P < 0.004$
TTP (months)	4.3 *vs.* 4.7	5.2 *vs.* 4.7	4.4 *vs.* 5.3	5 *vs.* 5.67	3.5 *vs.* 3.8	3.4 *vs.* 3.3	5.9 *vs.* 6.2
OS (months)	12.5 *vs.* 13.3	13.2 *vs.* 12.1	10.9 *vs.* 14.7 HR 0.77	13.3 *vs.* 14.5	12.4 *vs.* 13.4	12.2 *vs.* 10.3	12.4 *vs.* 12.2
Diarrhea (G3/4)	15.4% *vs.*13.9%	10.7% *vs.* 10.4%	7% *vs.* 10%	19% *vs.* 16%	21% *vs.* 16%	18% *vs.* 11%	18% *vs.* 14%
Mucositis (G3/4)	3% *vs.* 16% $P < 0.00001$	1.3% *vs.* 13.3% $P < 0.00001$	1% *vs.* 13% $P < 0.001$	1% *vs.* 12% $P < 0.001$	1% *vs.* 20% $P < 0.001$	2% *vs.* 16% $P < 0.001$	6% *vs.* 7%
Neutropenia (G3/4)	2.6% *vs.* 25.9%	2% *vs.* 19.8% $P < 0.00001$	2% *vs.* 32% $P < 0.002$	5% *vs.* 47% $P < 0.001$	1% *vs.* 56% $P < 0.001$	3% *vs.* 31% $P < 0.001$	0% *vs.* 4% $P < 0.035$
Hand-foot syndrome (G3)	18.1% *vs.* 0.7% $P < 0.00001$	16.2% *vs.* 0.3% $P < 0.00001$	–	–	–	–	–
Astenia (G3)	–	–	–	5% *vs.* 6%	–	–	11% *vs.* 5%
Total Bilirubin (G3/4)	17.3% *vs.* 5.4%	28.3% *vs.* 6.3% $P < 0.0001$	–	22% *vs.* 9% $P < 0.001$	39% *vs.* 22% $P < 0.001$	–	1.75% *vs.* 0.8%

FT, tegafur; UFT, uracil/tegafur; ORR, overall response rate; TTP, median time to progression; OS, median overall survival; HR, hazard ratio. In all studies, treatments were compared with the IV Mayo Clinic regimen of bolus 5-FU and LV.

i.v. administration [7]. Except for stomatitis, which showed a similar incidence, other severe non-hematological toxicities (diarrhea, asthenia, or nausea/vomiting) showed a lower incidence in the FT/LV treatment arm. Both treatment arms, FT/LV and 5-FU/LV, showed the same low number of toxic deaths: two in each arm. As expected, the gastrointestinal toxicity was the most characteristic of FT/LV regimen and it is also characteristic of 5-FU regimens modulated with LV. FT/LV produced diarrhea and mucositis with an incidence similar to that reported with other 5-FU prodrugs.

A great proportion of delays and dose reduction in the oral FT/LV arm was related to the fact that tegafur is administered daily during 21 days. Therefore, it was easier for toxicities appearing early during a cycle to delay or reduce dose treatment in the FT/LV arm. These tolerability results are significant from a clinical point of view, as chemotherapy in CRC patients is administered on a palliative basis and therefore safety is an important aspect to be considered due to its effects on the patients' quality of life. Other additional advantages found for oral 5-FU prodrugs in the treatment of advanced CRC are a clear preference of patients for oral chemotherapy [17,18], but also a reduction of the cost of treatment per patient and cycle compared to 5-FU/LV [21].

Several phase III studies have confirmed that infusional and not bolus 5-FU/LV is the optimal administration schedule in combination protocols with oxaliplatin and irinotecan [19,25]. Since oral fluoropyrimidines mimic a protracted infusional application of 5FU, they could serve as substitute for infusional 5FU/LV in combination protocols. Oral treatment has a more convenient application (no infusion pumps, no central venous devices), with good acceptance.

In conclusion, the results of this study show that oral tegafur plus LV is an effective chemotherapy that may be used alternatively to 5-FU/LV, alone or in combined regimens with new antitumoral agents for patients with advanced CRC. FT/LV provides a similar clinical benefit in terms of survival, has a good toxicity profile and is a more convenient application (no infusion pumps or no central venous devices are required). Future studies should evaluate the combination of oral tegafur/LV with other treatments.

Conflicts of interest statement

The authors have no conflicts of interest to disclose. Preliminary results of this study were presented at the 38th Annual Meeting of the American Society of Clinical Oncology (ASCO), Orlando, FL, May 19–21, 2002. Done in collaboration with Associació catalana per a la recerca oncològica i les seves implicacions sanitàries i socials (ACROSS), Barcelona, Spain and supported in part by a grant from Prasfarma – Grupo Almirall.

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