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CLINICAL TRIAL REPORT

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Protracted continuous infusion of 5-fluorouracil and low-dose leucovorin in patients with metastatic colorectal cancer resistant to 5-fluorouracil bolus-based chemotherapy: a phase II study

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Abstract Continuous-infusion (c.i.) 5-fluorouracil (5-FU) can overcome resistance to bolus 5-FU, and leucovorin (LV) enhances the cytotoxic effects of 5-FU, mainly when the duration of exposure to the latter is prolonged. The main objective of this study was therefore to determine the activity of a prolonged infusion schedule of 5-FU + LV in patients with metastatic colorectal cancer resistant to a 5-FU bolus-based chemotherapy. Only patients with metastatic measurable disease in progression during or within 2 months of the end of a 5-FU bolus ± LV-based chemotherapy were eligible for the study. 5-FU and l-LV were given as a 14-day c.i. every 28 days, the 5-FU dose being 200 mg/m^2 per day and the l-LV dose being 5 mg/m^2 per day. A total of 59 patients entered the study, of which 48 were resistant to 5-FU + LV and 11, to 5-FU + levamisole. Treatment was well tolerated, and WHO grade 3–4 toxicities were uncommon (11% of patients developed stomatitis and 7%, diarrhea). According to an intent-to-treat analysis, 10 of 59 patients obtained an objective response (1 complete response, 9 partial responses), for an objective response rate of 16% (95% confidence interval 8–25%). The median progression-free survival and overall survival were 4 and 9 months, respectively. The protracted 5-FU + LV c.i. schedule used in the present study is a well-tolerated and moderately active regimen in metastatic colorectal cancer patients resistant to 5-FU bolus ± LV. Only randomized studies can determine whether this palliative treatment has advantages in comparison with other second-line therapies such as 5-FU c.i. without LV, irinotecan, or oxaliplatin.

Key words 5-Fluorouracil · Continuous infusion · Colorectal cancer · Drug resistance · Advanced disease

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Introduction

Colorectal carcinoma is the second most common cancer in the Western world and is responsible for 10–11% of all cancer deaths [2, 7]. Unresectable metastatic disease can be palliated with chemotherapy, and the most frequently used agent is 5-fluorouracil (5-FU) in combination with leucovorin (LV) [1, 12, 15]. In most studies, 5-FU has been given as an i.v. bolus, and these studies have demonstrated that 5-FU bolus-based chemotherapy improves the survival and quality of life of patients with advanced disease [13]. However, the great majority of patients either do not respond to 5-FU bolus-based chemotherapy or become resistant after a brief initial response. In most cases these patients, have retained a good performance status, and an effective second-line chemotherapy regimen would be indicated.

Recent in vitro studies have suggested that the cellular target of bolus 5-FU is RNA and the target of continuous infusion (c.i.) 5-FU is DNA and, most importantly, that c.i. 5-FU might overcome resistance to bolus 5-FU [5, 27]. These observations have also been confirmed in clinical trials, which have demonstrated that prolonged 5-FU infusion maintains some activity in patients with metastatic disease pretreated with 5-FU bolus-based chemotherapy; unfortunately, response rates are low (10–15%) and the median overall survival is only 7–10 months [11, 20, 22, 29]. In these studies, LV was not added to 5-FU

c.i.; indeed, clinical trials have thus far demonstrated an increase in the activity of 5-FU when the latter is combined with LV, mainly when 5-FU is given as a bolus [29]. However, experimental studies suggest that LV, which potentiates 5-FU's effects on DNA through an enhanced inhibition of thymidylate synthase, might enhance 5-FU cytotoxicity more efficiently when cells are exposed to the latter for a prolonged period [16, 23, 25]. Indeed, several clinical studies have reported significant activity for 5-FU c.i. + LV combinations used in advanced colorectal cancer [4, 6, 17, 18, 28].

On the basis of these considerations we conducted a phase II trial in patients with metastatic colorectal cancer resistant to a 5-FU bolus ± LV-based chemotherapy to determine the activity of a protracted 14-day c.i. of 5-FU in combination with LV.

Patients and methods

Patients' selection

Eligibility criteria included: histologically confirmed diagnosis of colorectal adenocarcinoma, measurable metastatic disease, progression of disease during 5-FU bolus ± LV-based chemotherapy or within 2 months of its end, an Eastern Cooperative Oncology Group [ECOG] performance status (PS) of ≤2, a life expectancy of more than 2 months, a serum creatinine level of less than 1.6 mg/dl, a serum bilirubin level of less than 1.6 mg/dl, AST/ALT levels less than 2.5 times the normal values, a leukocyte count exceeding 3,500/μl, and a platelet count of greater than 100,000/μl. Patients with active infections, symptomatic cardiac disease, a recent history of myocardial infarction, and cerebral metastases were excluded. Approval for the study was obtained from the local ethics committee. All patients were informed of the nature of the study and gave their informed consent.

Treatment and study design

5-FU and LV were given as a 14-day c.i. at doses of 200 mg/m^2 per day for 5-FU and 5 mg/m^2 per day for LV (l-isomer form) as previously reported by Anderson et al. [3]. Treatment was repeated every 28 days unless progressive disease or life-threatening toxicity had occurred. The 5-FU dose was increased by 50 mg/m^2 per day if WHO grade ≥2 toxicity had not occurred in the previous cycle or was decreased by 50 mg/m^2 per day if WHO grade ≥3 toxicity had been observed in the previous cycle. Chemotherapy was carried out through an implantable central venous catheter using an external volumetric pump (Pharmacia Deltec CADD-PLUS, Pharmacia Deltec Inc., St. Paul, Minn., USA). The total weekly doses of 5-FU and LV were injected together in a 100-ml disposable reservoir and diluted in 0.9% NaCl up to a total volume of 100 ml.

Assessability, toxicity, and response criteria

Pretreatment evaluation included a medical history and physical examination, performance status assessment, complete blood cell count with differential and platelet counts, complete blood profile, determination of carcinoembryonic antigen (CEA), urinalysis, electrocardiogram, chest X-ray or computed tomography (CT) scan, abdominal CT scan and/or sonogram, and any other diagnostic procedure appropriate for the evaluation of metastatic sites. During treatment a physical examination was performed every 4 weeks; a complete blood cell count, every 4 weeks; and a blood profile, urinalysis, and CEA determination every 4 weeks. Sites of metastatic disease were revaluated every 8 weeks. A chest X-ray and/or an abdominal sonogram were repeated at least every 6 months if there was no evidence of lung or abdominal disease, respectively. Toxicity and responses were scored according to standard WHO criteria [21]. Duration of responses were calculated from the 1st day of treatment to the date of the first observation of progressive disease or the last examination.

Statistical analysis

To determine the number of patients to be included into the study the minimax two-stage design described by Simon [26] was used. The selected design parameters p0 (response rate in null hypothesis) and p1 (response rate in alternative hypothesis) were 0.10 and 0.25, respectively. Also, considering α and β errors of 0.05 and 0.10, respectively, the first stage of the study required 31 patients, and if at least 4 objective responses were observed the study required a total of 55 patients.

Results

A total of 59 consecutive patients with metastatic colorectal cancer entered the study. As shown in Table 1, where the patients' characteristics are summarized, the median ECOG PS was 1 (range 0–2), the predominant site of metastasis was the liver, 40 patients had multiple metastatic sites, and all patients had received prior 5-FU bolus-based chemotherapy. Overall, 34 patients had received 5-FU 370 at mg/m^2 per day by i.v. bolus plus l-LV at 100 mg/m^2 per day by i.v. bolus for 5 days, with treatment being repeated every 28 days; 14 patients had received 5-FU at 500 mg/m^2 per day by i.v. bolus once a week in the middle of a 2-h i.v. infusion of l-LV given at 250 mg/m^2; 11 patients had received 5-FU at 450 mg/m^2 per day by i.v. bolus for 5 days at 28-day intervals plus oral levamisole. In all, 48 patients (81%) had experienced progressive disease during 5-FU-based chemotherapy, as had 12 patients within 2 months of its end.

Table 1 Patients' characteristics

Characteristics	
Number of patients	59
Age (years):	
Median	60
Range	27–72
Sex:	
F/M	38/21
ECOG performance status:	
Median	1
Range	0/2
Primary site:	
Colon	41
Rectum	18
Number of metastatic sites:	
Single	19
Multiple	40
Prior chemotherapy:	
5-FU + LV	48
5-FU + ergamisol	11
Site of disease:	
Liver	44
Lung	22
Abdomen	34
Others	9

A total of 255 cycles of c.i. 5-FU + LV were delivered (median 5 cycles/patient; range 2–15 cyctes/patient). All patients were evaluable for toxicity, and the most frequently observed toxicities were stomatitis, diarrhea, nausea and vomiting, and dermatitis. Leukopenia of grade >1 was not observed. As shown in Table 2, toxicities were usually mild or moderate (WHO grade 1–2); grade III–IV toxicities consisted of stomatitis (11%), diarrhea (7%), and nausea and vomiting (4%). Two patients who experienced grade III–IV diarrhea required hospitalization. Toxic deaths were not observed.

According to an intent-to-treat analysis, all patients entered were evaluated for response. Of the 59 patients enrolled, 1 achieved a complete response and 9 achieved a partial response, for an objective response rate of 16% (95% confidence interval 8–25%). In all, 2 patients achieved a minor response, 21 had stable disease, and 26 were treatment failures (Table 3). The complete response was obtained in a patient with lymph node metastases who had received 5-FU bolus plus levamisole, and the remission lasted 8 months. Of the 9 patients who obtained a partial response, 1 had received prior adjuvant 5-FU + levamisole and 8 had received prior bolus 5-FU + LV-based chemotherapy for metastatic disease. The 9 partial responses occurred in the liver (4), in the lung (6), and in the abdominal nodes (4) and lasted a median of 9 (range 6–12) months.

The time to progression and survival distributions from the 1st day of therapy were estimated by the Kaplan–Meier method [14] and are shown in Fig. 1. The median time to progression was 4 months, and the median survival time was 9 months.

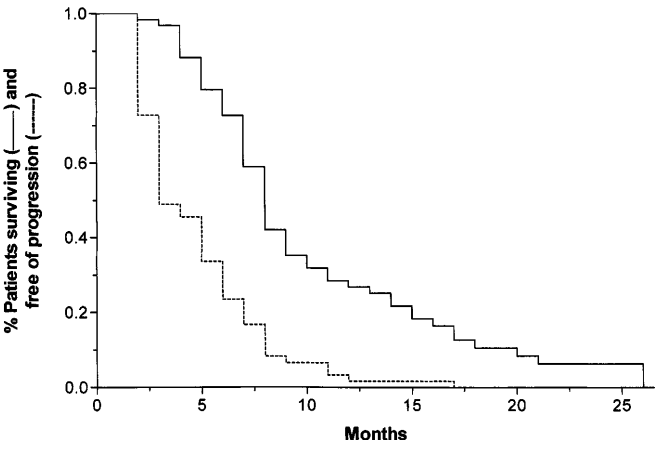

Fig. 1 Actuarial progression-free and overall survival curves

Discussion

Colorectal carcinoma is one of the most frequent cancers in the Western world and has a poor prognosis in the advanced stage. Although in recent years, new drugs such as oxaliplatin or irinotecan (CPT-11) or new 5-FU schedules such as high-dose 24- to 48-h or chronomodulated infusions have been developed [8, 10, 19], bolus 5-FU + LV remains a very commonly used first-line chemotherapy regimen. However, many patients either do not respond to this treatment or suffer disease progression after achieving an initial response. In vitro studies have demonstrated that the mechanism of resistance to bolus 5-FU is different from that underlying resistance to c.i. 5-FU; indeed, in cells that are resistant to short-term exposure to 5-FU, a prolonged period of exposure achieves significant cell kill due to the different mechanisms of action found between "pulse" and protracted-exposure 5-FU: the RNA effect for pulse 5-FU versus thymidylate synthase inhibition and the DNA effect for protracted-exposure 5-FU [5]. Clinical trials have confirmed these preclinical observations, showing some activity for protracted c.i. 5-FU in patients pretreated with 5-FU bolus-based chemotherapy as reflected by response rates in the range of 10–15% [11, 20, 22, 29]. In addition, LV increases 5-FU-induced inhibition of thymidilate synthase and enhances the tumor cell kill, mainly when the duration of 5-FU exposure is prolonged [16, 23, 25], and clinical trials have demonstrated that c.i. 5-FU in combination with oral or i.v. LV has significant activity in patients with previously untreated metastatic colorectal cancer [4, 6, 17, 18, 28].

On the basis of these in vitro and clinical studies we decided to evaluate the activity of 5-FU given as a prolonged c.i. in combination with LV to patients with metastatic colorectal cancer resistant to 5-FU bolus ± LV-based chemotherapy. The results demonstrate that the combination of 5-FU + LV we used was well tolerated, with only 7% and 11% of patients developing grade III–IV diarrhea and stomatitis, respectively, and that it possesses moderate but definitive activity in patients resistant to bolus 5-FU ± LV. Indeed, we obtained an objective response rate of 16% and observed a minor response or stable disease in 42% of patients without a significant difference between patients who

Table 2 Overall worst toxicity (59 patients evaluable)

Adverse event	WHO grade (%)			
	1	2	3	4
Stomatitis	29	17	9	2
Diarrhea	14	8	6	1
Nausea/vomiting	18	9	4	0
Dermatitis	18	9	0	0
Conjunctivitis	20	8	0	0

Table 3 Objective responses (59 patients evaluable)

Response (WHO)	Number of pts (%)
Complete response	1 (2%)
Partial response	9 (14%)
Complete + partial responses	10 (16%)
Minor response	2 (3%)
Stable disease	21 (36%)
Treatment failure	26 (45%)
Total	59 (100%)

had previously received 5-FU + levamisole or 5-FU + LV. The median overall survival was 9 months. When these results are compared with those obtained with 5-FU given by prolonged c.i. without LV or with CPT-11, they are not very different [11, 24]. However, both the response rate and the median survival lie in the upper range of the results obtained using 5-FU alone or with CPT-11, although all patients included in our study were in progression during or within 2 months of the end of 5-FU chemotherapy and were therefore highly resistant to bolus 5-FU. Instead, in many studies using 5-FU c.i. alone or with CPT-11 the degree of resistance to bolus 5-FU was not specified.

In conclusion, c.i. 5-FU + LV as used in the present study is a well-tolerated and moderately active regimen in patients with metastatic colorectal cancer resistant to 5-FU bolus ± LV, but a clear superiority over 5-FU c.i. alone or other second-line treatments such as CPT-11 is not evident. Only randomized studies can determine which is the best palliative treatment in this patient population. A recent randomized study indicates that CPT-11 might be slightly, albeit significantly, superior to c.i. 5-FU in terms of survival and progression-free survival [30]; however, no difference in quality of life was observed between the two arms, and a significant number of patients (22%) randomized to c.i. 5-FU had previously progressed during or within 3 months of the end of a c.i. 5-FU-based regimen. Therefore, in 5-FU bolus-resistant patients, c.i. 5-FU may yet represent an acceptable alternative. Finally, several phase II studies in 5-FU-resistant colorectal cancer patients have also demonstrated activity similar to that of CPT-11 or c.i. 5-FU for a new platinum derivative, oxaliplatin, when given either alone or in combination with c.i. 5-FU + LV [9]; therefore, randomized phase III studies are needed to compare it in terms of survival and quality of life with other second-line treatments in 5-FU-resistant patients.

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