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High-dose Folinic Acid and 5-Fluorouracil Bolus and Continuous Infusion in Advanced Colorectal Cancer

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Abstract—*An enhanced antineoplastic effect of 5-fluorouracil in patients with advanced colorectal cancer has been produced either by combination with folinic acid or administration by continuous infusion.*

Thirty-seven patients with advanced measurable colorectal cancer received high-dose folinic acid (LV 200 mg/m^2) followed by 5-fluorouracil i.v. bolus (300 mg/m^2) and continuous infusion (300 mg/m^2) on days 1 and 2 then 14 and 15 every 4 weeks. In the absence of toxicity, 5-FU was increased to 400 mg/m^2 i.v. bolus and continuous infusion at course 2 and to 500 mg/m^2 at course 3 and from course 4 maintained at 500 mg/m^2. Responses were: complete responses: 1 (2.7%), partial responses: 19 (51.4%), no change: 8 (21.6%) and progressive disease: 9 (24.3%). CEA decrease was correlated with response. Median duration of response was 11 months. Median survival was 18 months, 21% of the patients were alive at 2 years. Toxicity was low, with diarrhea in 17% and nausea in 11.5% of the patients.

LV-5-FU bolus and continuous infusion is safe and has definite activity in metastatic colorectal cancer.

INTRODUCTION

5-FLUOROURACIL (5-FU) i.v. bolus has been the standard therapy for advanced colon cancer for more than 20 years. Objective responses are observed in 20% of patients. Recently, an enhanced cytotoxicity of 5-FU has been demonstrated using either leucovorin (LV) pretreatment [1, 2] or continuous infusion [3].

LV increases inhibition of thymidylate synthetase by the active metabolite of 5-FU: fluorodeoxyuridinemonophosphate (FdUMP). Clinical trials including more than 30 patients have shown an increased response rate ranging from 18 to 40% [4]. Furthermore, a randomized study comparing LV–5-FU to 5-FU has demonstrated a higher response rate for LV–5-FU, 48% vs. 11% [5]. However, the optimum dose and schedule of drug administration is not known and toxicity requires a 5-FU dose lower than standard i.v. bolus.

Continuous 5-FU infusion appears more toxic [6] but produces a higher response rate than i.v bolus: 32% [7], 44% [8]. Continuous infusion allows administration of higher monthly 5-FU dose than i.v. bolus. Another study has shown that increasing the frequency of 5-FU administration intensified the tolerable dose [9]: the maximum dose was 30 mg/kg/24 h, 48-h infusion every week, which produced a response rate of 30%.

The present study was designed to combine these different improvements in 5-FU therapy and to minimize toxicity: LV was administered first, followed by 5-FU i.v. bolus and continuous infusion, every 2 weeks.

PATIENTS AND METHODS

Patients

Patients with the following criteria were eligible in this prospective study: histologic proof of colorectal adenocarcinoma, measurable metastatic or unresectable cancer, WHO performance status 0–3, life

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expectancy of at least 10 weeks and no history of previous chemotherapy. This study extended over the period from February 1985 to February 1987.

Treatment

Doses and schedule were determined after a phase I study. This study showed that bolus and continuous infusion allowed one to administer higher 5-FU doses than the bolus alone and that a 2-week interval between drug administration permitted one to avoid most toxicities of monthly courses. At the first course, patients received LV 200 mg/m^2 i.v. in a 2-h infusion, followed by 5-FU 300 mg/m^2 i.v.bolus then 5-FU 300 mg/m^2 in a 22-h infusion on day 1 and the whole procedure was repeated on day 2. The same dose and schedule of LV and 5-FU were repeated on day 14 and day 15. The second course was administered 4 weeks after day 1 (day 29 = day 1) and the 5-FU bolus and infusion dose was increased to 400 mg/m^2 if the WBC count was over 4000/mm^3, the platelet count over 120,000/mm^3 and toxicity tolerable (WHO grade 0–1). The 5-FU bolus and infusion dose were increased to 500 mg/m^2 for the third and consecutive courses if toxicity remained tolerable. Before treatment, a totally implantable infusion device was implanted. Some patients were treated on an outpatient basis using portable pumps. The 5-FU dose was reduced of 100 mg/m^2 in cases of toxicity. Patients continued on therapy until disease progression or 9 months in cases of no change or until no change at two consecutive evaluations from the sixth month in the case of response. In responders, treatment was readministered in cases of disease progression after cessation of therapy.

Study parameters

Physical examination and complete blood cell counts were performed every 2 weeks. CEA when normal, liver function tests, chest X-ray, computed tomographic or ultrasonic scans were repeated at 12-week intervals. CEA was repeated at monthly intervals if it was increased.

Measurable lesions included lesions that could be defined by imaging procedures. Serosal effusions or CEA levels were not considered as measurable disease. Complete response (CR) was defined as a complete disappearance of all clinically evaluable disease, partial response (PR) as a decrease of at least 50% of the sum of the products of the diameters of measurable lesions. No change (NC) was defined as a decrease not reaching 50% or an increase of less than 25% and progressive disease (PD) was an increase of no less than 25%. CEA levels were not used to assess response.

Relapse was defined as at least 25% increase in a patient previously classified as having a response.

Response duration and survival were calculated from the beginning of chemotherapy using the Kaplan–Meier method, the end-point was November 1987. The log-rank test was used to compare patient survival according to pretreatment characteristics.

RESULTS

Patient characteristics

Thirty-seven patients with advanced colorectal cancer were entered in this series. The pretreatment characteristics of the patients are shown in Table 1. Fifteen had exclusive liver metastases, three lung metastases, six abdominal tumor. Thirteen patients had multiple metastases. Twenty-nine patients had histological documentation of metastasis. Five patients with rectal cancer previously received pelvic radiotherapy. In these patients, evaluable metastases were outside the pelvis.

Responses

There were one CR (2.7%), 19 PRs (51.4%), eight NCs (21.6%) and nine PDs (24.3%). CR was observed in a 52-year-old woman with malignant ascitis, a 2 cm biopsy-proven measurable pelvic mass, a pretreatment moderate increase of CEA level which normalized during therapy. Treatment lasted 9 months and CR 17 months. Survival reached 23 months. No response was observed in five patients who were initially responders when treated was readministered.

Pretreatment characteristics did not significantly affect the response, except CEA levels (Table 2). In patients with pretreatment elevated CEA, over 50% decrease at any time during therapy was observed in 15/32 (47%). CEA correlated with response: 13/15 (87%) with >50% CEA decrease were responders, 2/2 with CEA decrease less than 50% and only 2/15 (15.4%) with CEA increase or stable. Three of five (60%) with normal CEA were responders. A >50% decrease in CEA predicted response with 76.5% sensibility and 76.4% specificity.

Alkaline phosphatases declined in 7/14 patients (50%). Six of seven with decrease of alkaline phosphatases were responders.

Five responses were observed among 10 patients who could not receive the maximum 5-FU dose.

Sixteen responses were observed at 3 months, three at 6 months and one at 9 months.

Survival

Median survival was 18 months, with 64% alive at 1 year and 21% at 2 years. Responders had a median survival of 21 months. Median survival was 12 months in case of NC and 7 months in case of PD.

Sex, age, performance status, mass dimension, liver or other sites of metastases, pretreatment alkaline phosphatases and the dose of 5-FU did not

significantly affect the survival (Table 2). CEA over 10 times the normal value almost reached a significant level, $P = 0.07$.

The median duration of responses was 11 months with 37% remaining responders at the 12th month. One patient remained a responder at the 23rd month.

Toxicity

Toxicity was moderate and controllable by reducing the dose of 5-FU. The most frequent toxicities were nausea (11.5%) after 5-FU i.v. bolus, manageable with metoclopramide, and diarrhea which did not require intravenous hydration (17%).

The most severe toxicities occurred at the same

Table 1. Pretreatment characteristics of 37 patients

Median age	61.5 years S.D. 8.4 years (range 38–79)
Sex	
male	18
female	19
Primary cancer	
colon	29
rectum	8
WHO performance status	
0	8
1	16
2	12
3	1
Mass diameter (largest mass)	
<2 cm	6
2–5 cm	8
5–10 cm	8
>10 cm	15
Site of metastases	
liver	25
lung	9
abdominal mass	13
bone or skin	5
CEA	
normal	5
normal limit × 1–10	14
normal limit × 10–100	11
normal limit × >100	7
alkaline phosphatase	
normal	23
increased	14

Table 2. Responses and median survival according to pretreatment characteristics

	Response CR + PR %	P χ^2	Median survival months	log-rank
Sex				
male	61	NS	13	NS
female	47		18	
Age				
<62 years	53	NS	15	NS
>62	55		18	
Performance status (WHO)				
0–1	58	NS	18	0.15
2–3	46		13	
Site				
liver	53		18	
liver + other	56	NS	18	NS
ex liver	50		20	
Mass				
<5 cm	57	NS	18	NS
>5 cm	52		15	
CEA				
1–10 *N*	58	NS	20	0.07
>10 *N*	50		13	
Alkaline phosphatases				
N	61	NS	15	NS
increased	43		18	

Table 3. Toxicity

	n	%
Alopecia >50%	1	3
Nausea–vomiting	5	14
Diarrhea	6	16
Skin-rash or hand-foot syndrome	5	14
Granulopenia <500/mm^3	1	3

time in a single patient receiving the maximum 5-FU dose: granulopenia below 500/mm^3 and hair loss >50%. Toxicity in this patient was due to protocol violation when receiving 5-FU 500 mg/m^2 instead of 300 mg/m^2 at course 3; this patient had mild toxicity at course 2. Toxicities are reported in Table 3.

Seventy-three per cent of the patients received the maximum 5-FU dose for the third course. There was no drug-related toxic death.

DISCUSSION

This study confirms the antitumoral activity of LV–5-FU bolus and continuous infusion in metastatic colorectal cancer. Two recent studies and a recent paper which reviewed the earlier reports of LV–5-FU showed that the response rate in patients with no prior chemotherapy ranged between 18% and 43% in eight series including more than 30 patients [4, 10, 11]. Furthermore, it was proven in randomized trials that LV–5-FU is superior to 5-FU alone [5, 12]. However, little is known about optimum dose and schedule: monthly LV doses varied from 25 to 3000 mg/m^2, 5-FU from 550 to 4800 mg/m^2 and frequency was either weekly, every 3 weeks, or monthly for 4 or 5 consecutive days or 4–5 days continuous infusion. The pharmacokinetics of reduced folates suggested that the active level is 10 μmol/l which was achieved either with LV 500 mg/m^2 for 6 consecutive days [12, 13] or LV 200 mg/m^2 bolus for 5 consecutive days [14]; response rates were respectively 9% in pretreated patients or 45% in patients without prior chemotherapy with the first regimen and 39% in patients without prior chemotherapy with the second regimen. The most common LV dose is 200 mg/m^2 bolus 4–5 times a month [4]. LV is composed of equal amounts of *d*- and *l*-diastereoisomers, the *l*-isomer is the active form [15]. Further progress in 5-FU modulation could result from the use of the *l*-isomer of folinic acid administered alone.

Toxicity limits the 5-FU boluses to a rather low dose (350–400 mg/m^2) when used during 4 or 5 consecutive days [3, 4]. Laufman *et al.* reported equal efficacy with less toxicity using a weekly schedule [4]. Another weekly schedule was also used by Hines *et al.* who reported a high response rate: 45% in a study including 87% of pretreated patients. This regimen consisted in LV 500 mg/m^2 and 5-FU 600 mg/m^2 weekly [16].

In this series of 37 patients, we use the 'standard' LV dose followed by a 5-FU bolus comparable to boluses used in a LV bolus–5-FU bolus combination. Our schedule of 2 consecutive days every 2 weeks allowed us to add administration of 5-FU by continuous infusion. The 5-FU monthly dose reached 4000 mg/m^2 in 72% of the patients. Toxicity was easily manageable and rather low due to the frequency of administration. Our objective response rate of 54% (S.D. 36–72%) appears higher than that reported by authors using LV–5-FU bolus–bolus but needs confirmation, then randomization to demonstrate a superiority. The CEA decrease appeared well correlated with response as observed by others [4].

Our median survival of 18 months appears to be higher than that reported with the other LV–5-FU regimens ranging from 8 to 15 months [10–14, 17]. However, such a comparison without a control group is hazardous and could be due to differences in the populations studied. Median survival in responders was 21 months, in NC 12 months and in PD 7 months. Such a survival in NC and PD is unusually favorable and could be in part due to the therapeutic value of the regimen used, especially in

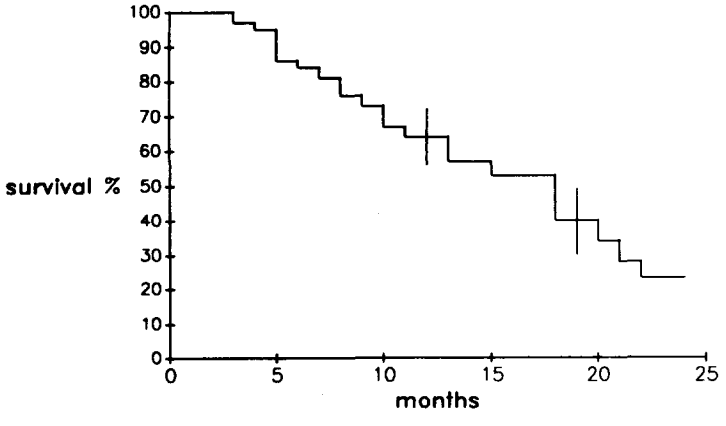

Fig. 1. Survival of 37 patients with advanced colorectal cancer treated with LV and 5-FU bolus and continuous infusion (vertical hash marks indicate S.D.).

the case of no change. Other data suggesting a relatively high therapeutic effect of the regimen used is the median survival over 1 year in patients with a poor prognosis at the onset of chemotherapy such as patients with performance status 2–3 and masses over 5 cm.

In our opinion, LV–5-FU bolus and continuous infusion represents a real improvement in the therapy of advanced colorectal cancer.

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