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Randomised Comparison of Weekly Bolus 5-Fluorouracil With or Without Leucovorin in Metastatic Colorectal Carcinoma

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148 patients with advanced untreated colorectal cancer were randomised to receive a weekly bolus of 5-fluorouracil (5-FU) 600 mg/m² alone, with or without leucovorin (LV) 500 mg/m². 5-FU plus LV produced a higher response rate than 5-FU alone: 23% (5 complete response, 11 partial response) vs. 8% (2 complete response, 4 partial response) ($P = 0.03$) out of 70 and 72 evaluable patients, respectively. Median survival was 11 months in both groups and median time to progression was not significantly different ($P = 0.08$). The combined regimen was more toxic than 5-FU alone, as evidenced by (a) a higher percentage of grade 3–4 diarrhoea, 19.5% vs. 8.5% ($P = 0.045$) and conjunctivitis, 26.5% vs. 5.6% ($P = 0.0025$); (b) the recording of one toxic death in the combined arm; and (c) the reduction of the median dose intensity of 5-FU actually delivered during the first 2 months of treatment. We conclude that 5-FU plus LV at a price of a higher toxicity is more active than 5-FU alone without improving survival and progression-free survival.
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INTRODUCTION

5-FLUOROURACIL (5-FU) remains the standard drug for the treatment of advanced colorectal cancer, even if response rates are not superior to 20%. Experimental studies have shown that 5-FU cytotoxicity can be potentiated by folinic acid (FA). The inhibition of the target enzyme thymidilate synthetase (TS) is induced by a covalent ternary complex with the 5-FU metabolite 5-fluorodeoxyuridilate (FdUMP) in the presence of L-5, 10-methylenetetrahydrofolate (CH_2FH_4). The stability of the ternary complex can be increased by giving exogenous leucovorin (LV) which is metabolised to CH_2FH_4 [1]. The interest for 5-FU modulation is documented by the number of phase I–II studies, which suggest the increased clinical activity of the combination and confirm the soundness of the underlying biochemical rationale [2–4]. However, after almost 10 years since its first clinical testing, the 5-FU plus LV combination remains a controversial issue [5]. According to the clinical literature an apparent consensus exists on the superiority of 5-FU plus LV in terms of objective response, while no agreement emerges in terms of extension of survival, improvement of quality of life and activity in previously treated patients [6]. In

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addition, LV is also recognised to enhance 5-FU toxicity, mainly stomatitis and diarrhoea.

The 5-FU modulation has been tentatively transferred to the clinic with various dosages and schedules, of which the two classic ones are the 'weekly bolus' and the 'daily × 5 month'. Most of the published studies employed a 5-day regimen of 5-FU every 5 weeks, with a range of LV from 20 to 500 mg/m^2; three studies used a weekly schedule of 5-FU plus LV [6]. So far, no randomised study has compared the weekly bolus administration of 5-FU (600 mg/m^2) with the same dose and schedule of the fluoropyrimidine plus high-dose LV. Following our preliminary report [7], we present here the final analysis of a randomised comparision of 5-FU plus LV vs. 5-FU alone, where the fluoropyrimidine is given by weekly bolus at the same dose in both arms.

PATIENTS AND METHODS

The study protocol required that all patients had to have histologically confirmed, metastatic or recurrent colorectal carcinoma that was beyond surgical eradication. Patients with previous histological confirmation of a primary colorectal cancer, when they had developed radiographic evidence of multiple pulmonary metastasis with no other accessible lesions for biopsy, were also included. Patients who received adjuvant 5-FU were excluded from the study. The indicator lesions were to be bidimensionally measurable by physical examination or radiographic measurement. Peformance status, according to Eastern Cooperative Oncology Group (ECOG) score, was ≤ 2. Adequate platelet ($> 100\,000/\mu l$) and white blood cell (WBC) counts ($> 4000\ \mu l$) as well as normal renal function and total bilirubin (< 2 mg/dl) were required. Radiation therapy was allowed provided that no indicator lesion was irradiated and that at least 4 weeks had elapsed after irradiation of the axial skeleton.

An informed consent was required from every patient before entering the study.

Treatment plan

The control 5-FU arm consisted of a weekly bolus of 600 mg/m^2 without a loading course. Treatment was continued until evidence of progression or, in the case of complete response (CR), for a minimum of 2 months after establishing the response. In the 5-FU plus LV regimen, 600 mg/m^2 of 5-FU were administered as an intravenous bolus 1 h after the beginning of a 2-h infusion of 500 mg/m^2 of LV diluted in 250 ml of normal saline. Our protocol differed from the original Roswell Park Memorial Institute regimen [8] in that no 2-week rest periods were planned after 6 weekly treatments. No dose reduction was planned for LV and 5-FU. In case of cytopenia, diarrhoea or stomatitis (WHO grade 2 or greater), treatment was withheld until complete recovery with WBC $> 3000/\mu l$ and platelets $> 100\,000/\mu l$. The calculation of actually delivered doses was based on the following rules. The time frame began on the day of the first drug administration and ended 7 days after the last drug administration. Dose intensities were calculated for the first eight treatment cycles, as all responses observed in this trial occurred within the first 2 months of treatment.

Response criteria

CR required total disappearance of all tumours initially observed. Partial response (PR) required a 50% reduction in the sum of the products of the maximum perpendicular tumour diameters lasting at least 8 weeks of all lesions measured on chest X-ray, computed tomography and ultrasonogram. An adjunctive clinical criterion was the evaluation of hepatomegaly, which was acceptable as a measurable lesion if the liver edge extended at least 5 cm below the costal margin at the middle clavicular line or below the xyphoid process. Hepatomegaly response required a greater than 30% decrease in the sum of the measurements, and in any case ultrasonography was mandatory for the final response evaluation. No new areas of malignant disease should have appeared during the period of tumour regression.

Stable disease (SD) was defined as less than 50% reduction or less than 25% increase in the sum of the products of maximum perpendicular tumour diameters with no new lesions appearing during at least 2 months of treatment.

Method of randomisation

All patients were randomised by calling the trial office at the Istituto Nazionale per la Ricerca sul Cancro in Genoa. Treatment allocations were balanced in blocks of varying size (10–12 patients). Specific lists of randomisation were available for each participating centre. No other stratification parameter was used.

Statistical analysis

The study was planned to detect a 20% improvement in objective response for patients on the combined 5-FU plus LV arm. A type 1 error rate of 0.05 and a type 2 error rate of 0.2 (power 0.80) was used to calculate a sample size of 70 patients for each arm. Other endpoints were survival and progression-free survival. Treatment differences in objective response rates were analysed using standard χ^2-test for heterogeneity. All P-values were derived from a two-sided test for significance. Difference in toxicity was analysed by means of χ^2-test for trend [9]. The Kaplan–Meyer method was used to estimate progression-free survival and overall survival. Survival and progression-free survival were measured from randomisation to disease progression or death due to whatever cause. The statistical significance of treatment difference was assessed by the logrank test [10].

RESULTS

From August 1984 to January 1990, 148 patients entered the study. The patients' characteristics according to treatment arms are shown in Table 1. The median ECOG performance status (PS) was 1 in the 5-FU plus LV arm, 0 in the 5-FU arm. Cancer of the rectum was the site of primary tumour in almost half of the patients; this is a much higher percentage than that reported in most other randomised comparisons in this disease. There were more men than women in the 5-FU plus LV arm and median age was 61 years in both groups. The other major characteristics, including sites of metastasis and number of disease sites, are well balanced.

Dose intensity

Table 2 reports the analysis of 5-FU dose intensity actually delivered to the patients during the first 4 and 8 weeks of treatment. This analysis was not planned in the protocol and the 8-week time period was selected upon observing that all responses in this study occurred during the first 2 months of treatment, i.e. no patient with stable disease after 8 weeks of therapy had an objective response upon treatment continuation. Only 20% of patients receiving 5-FU plus LV completed the first 2 months of therapy without delays, in contrast to 55% of patients receiving 5-FU alone (data not shown). The median 5-FU dose intensity actually delivered in the two arms was similar

Table 1. Patient characteristics by treatment regimen

	5-FU (n = 73)	5-FU+LV (n = 75)
Sex		
Male	35	45
Female	38	30
Age (years)		
<50	8	10
51–69	51	51
>70	14	14
Performance status		
ECOG 0	40	26
ECOG 1	25	35
ECOG 2	8	14
Site of primary tumour		
Colon	37	36
Rectum	34	38
Not specified	2	1
Site of metastases		
Liver only	39	35
Liver and pelvis	9	8
Liver and lung	5	4
Liver and other	11	10
Lung only	6	9
Lymph nodes	0	2
Pelvis only	2	0
Pelvis and other	1	7
No. of disease sites		
1	49	49
2	18	21
3 or more	6	5

after 4 weeks, but it was 20% lower after 8 weeks of treatment in the 5-FU plus LV arm.

Toxicity

Table 3 summarises the toxicity data. The haematological toxicity of both treatment regimens was very mild, with no grade 3–4 leukopenia or thrombocytopenia. Alopecia was minimal as well. The major toxicities were diarrhoea, stomatitis and conjunctivitis. All of them were more than twice as frequent in patients treated with 5-FU plus LV than in those receiving 5-FU alone: 19.5 vs. 8.5% grade 3–4 diarrhoea (P = 0.045), 19.4 vs. 9.8% grade ≥ 1 stomatitis (P = 0.12) and 26.5 vs. 5.6% conjunctivitis (P = 0.0025), respectively. Untreatable diarrhoea with haemodynamic impairment was the cause of the single toxic death reported in this study. This side-effect developed after the seventh weekly cycle of 5-FU plus LV in a 69-year-old patient who was not promptly hospitalised. Interestingly, the patient had tolerated chemotherapy very well until that time.

*Table 2. Delivered dose intensity**

	First 4 weeks		First 8 weeks	
	5-FU	5-FU+LV	5-FU	5-FU+LV
Median (mg/m²/week)	600	600	600	505
Mean (mg/m²/week)(S.D.)	590 (43)	544 (85)	549 (86)	461 (128)

*The calculation of delivered dose intensity began on the day of first drug administration and ended 7 days after the fourth and eighth treatment administration.

Table 3. Toxicity

	% of patients	
Toxicity	5-FU	5-FU+LV
Leukopenia		
<4000/ml	11.3	15.3
<2000/ml	0.0	0.0
Thrombocytopenia		
<100 000/ml	4.2	5.6
< 50 000/ml	0.0	0.0
Nausea/vomiting		
Grade 1–2	39.5	34.7
Grade 3–4	0.0	4.2
Diarrhoea		
Grade 1–2	26.8	29.1
Grade 3–4	8.5	19.5
Stomatitis		
Grade 1–2	8.4	16.6
Grade 3–4	1.4	2.8
Conjunctivitis†	5.6	26.5
Alopecia (mild)	0.0	4.2
Cutaneous		
Hyperpigmentation	0.0	7.0
Dermatitis	1.4	7.0

*$\chi^2_{1,t}$ = 4.01; P = 0.045.
†$\chi^2_{1,t}$ = 9.11; P = 0.0025.

Objective response

The overall response status is shown in Table 4. 5-FU plus LV produced a higher response rate than 5-FU alone; 22.9 [95% confidence interval (CI) : 13.1–32.7] vs. 8.3% (95% CI : 2.0–14.6), respectively (P = 0.03) (χ^2 adjusted for balanced performance score; P = 0.028). Five CR and 11 PR out

Table 4. Overall response status for evaluable patients

	5-FU		5-FU+LV	
Patients randomised	73		75	
Patients never treated	0		3	
Treatment refusal	0		2	
Lost to follow-up	1		0	
	No.	%	No.	%
Patients evaluable for response	72		70	
Complete response	2	2.8	5	7.2
Partial response*	4	5.5	11	15.7
Overall response (95% CI)	6	8.3	16	22.9
Stable disease	38	52.8	27	38.6
Progressive disease	28	38.9	27	38.5

*χ^2_h = 4.66; P = 0.03

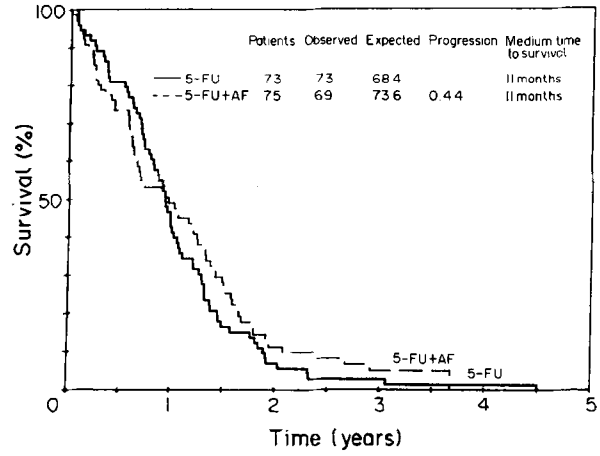

Fig. 1. Actuarial survival curves.

of 70 evaluable patients were observed in the 5-FU plus LV treatment group, compared to two CR and four PR out of 72 patients in the 5-FU group.

Stable disease was the most frequent response category. 38% of patients treated with the combination and 53% receiving 5-FU alone had stable disease. The percentage of treatment failures was equivalent in both treatment arms (40%). Responses occurred more frequently in patients with rectal cancer than in patients with colon cancer. In fact, the site of primary tumour in 14 of the 22 responders and in 4 of the 7 complete responders was the rectum (data not shown). This difference did not reach statistical significance.

No specific metastatic site appeared to respond better than others; the seven CR occurred in patients with liver disease only (3 patients), lung disease only (2 patients), liver and lung (1 patient), and liver and pelvis (1 patient).

Survival and progression-free survival

142 patients out of 148 randomised (96%) have died and the minimum follow-up time of the survivors is 18 months. No difference in survival was observed between the treatment groups. The median survival time was 11 months in both groups of patients (Fig. 1). The median time to failure (Fig. 2) was longer for the 5-FU plus LV arm (5 months) than for the 5-FU arm (3 months only), but this difference did not reach statistical significance ($P = 0.082$).

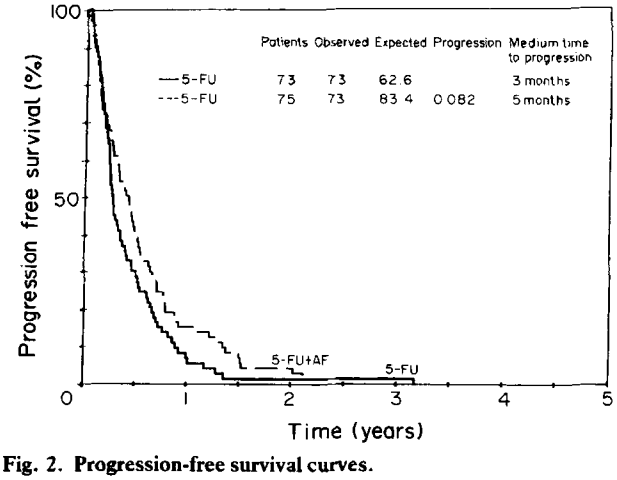

Fig. 2. Progression-free survival curves.

DISCUSSION

Our trial, among the nine published phase III randomised comparisons of 5-FU vs. FU plus LV in colorectal cancer, can be singled out as the only one comparing the identical weekly bolus schedule and dose of 5-FU in both arms. In spite of the differences in schedule and dosage, our results, in terms of response, are similar to those of five other studies comparing 5-FU with or without LV: the combination, irrespective of LV dose, is more active, but more toxic than 5-FU alone [8, 11–14]. The three remaining studies contradict the general trend, being negative in terms of response [15–17].

Our objective response rate to 5-FU alone of only 8% is much lower than that classically reported in the trials of the 1960s and 1970s. These data are in keeping with the results of the most recently published literature and lead us to consider questionable the concept of dose intensity of 5-FU given as a bolus. According to the dose intensity/response theory, an increase from 500 to 600 mg/m^2 weekly produces an increase in response rate from 20 to 29% [18]. On the contrary, in nine randomised studies (including ours) conducted on approximately 1000 patients, no correlation between dose intensity and response is evident, since the response rate ranges from 8 to 19%, irrespective of the therapeutic dose (500 or 600 mg/m^2/week) of 5-FU administered [8, 11–17].

The superior activity of the combination is better evidenced in our study on the following grounds: the dose intensity analysis shows in the 5-FU plus LV arm a 20% decrease of the median actual dose intensity, due to delays, forced by toxicity; the initial randomisation imbalance favours the 5-FU arm with fewer males and better performance status—better prognosis patients. Since our study is the only one where the 5-FU control arm had the antimetabolite given as a weekly bolus, it is reasonable to conclude that the potentiation by FA is independent from the schedule of 5-FU administration.

The enhanced activity of the combination is unable to prolong survival in our patients, in line with the majority of the studies, with two exceptions [11, 12]. Since the number of responding patients is less than 1/5 of the overall group, this data can be related to a 'dilution effect'. The failure to impact on survival is in part explained by the relatively small number of patients accrued to this trial, which was designed with response as the main endpoint. It is also to be stressed that only in the 5-FU plus LV arm 5 patients did not receive any treatment, and these could have a bearing together with the overall poorer performance status of the 5-FU plus LV arm on survival. In fact the NCCTG study, which did show an effect on survival, included a large number of non-measurable and presumably low-volume disease. The definite answer as to whether 5-FU and LV should be considered the treatment of choice for colon cancer awaits a final meta-analysis, including all the published phase III studies, which is now being carried out [19].

There is as yet no consensus about the best dose and schedule. The two most commonly used schedules, i.e. weekly bolus or daily bolus × 5 month, differ substantially in terms of toxicity [20]. The dose-limiting toxicity is diarrhoea in the former [21], and mucositis in the latter [3]. Diarrhoea has been recognised as the major cause of toxic deaths in all these trials [22]. The common toxicity pattern, along with the low response rate obtained in our trial with 5-FU plus LV given by weekly bolus, leads us to consider the daily × 5 month schedule more appropriate for future trials both in advanced and adjuvant therapy.

In addition to the problem of the schedule remains the issue

of the best LV dosage. In two of the six phase III studies, establishing the superiority of the combination in terms of response, a low (20–25 mg/m^2) and a high (200–250 mg/m^2) dose of LV were compared with 5-FU alone. While one study found little efficacy in the low dose [13], the second unexpectedly showed that the highest response rate was associated with low-dose LV [12]. We are therefore left with the conflicting information that the low LV dose is more apt to enhance the biochemical modulation of a 5-day 5-FU regimen, as used by NCCTG, while the high dose is more suited to increase the efficacy of a weekly schedule, as used by GITSG. In an attempt to answer the question of which of the two regimens is superior, a recent randomised study found no difference in response and survival between a 5-day 5-FU bolus (425 mg/m^2)–low-dose LV (20 mg/m^2) regimen and a weekly 5-FU bolus (600 mg/m^2)–high dose LV (500 mg/m^2), but the authors stress the decreased toxicity and cost of the 5-day low-LV regimen [23]. Since, according to our data, 600 mg/m^2 of bolus 5-FU is too high a dosage and needs a reduction to 500 mg/m^2, this study cannot clarify whether the lesser toxicity is due to the decreased dosage of LV or to the high-bolus 5-FU used in the weekly schedule; anyway, the reduced cost of the low-LV regimen supports its use.

In conclusion, our study adds new evidence to confirm the increased activity of the 5-FU plus LV combination, but we are still far from effectively tackling the advanced disease, and new solutions need to be scrutinised.

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