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Short Communication

Treatment of Advanced Colorectal Cancer with High-dose Intensity Folinic Acid and 5-Fluorouracil Plus Supportive Care

R. Petrioli,[1] M. Lorenzi,[2] A. Aquino,[1] S. Marsili,[1] B. Frediani,[1] V. Palazzuoli,[3] G. Marzocca,[4] G. Botta,[2] F. Tani,[2] A. De Martino,[2] W. Testi,[2] C. Setacci,[5] F. Salvestrini,[5] D.De Sando,[6] S. Bovenga,[6] L. Mariani,[6] S. Mancini,[2] G. Tanzini,[5] S. Armenio,[5] E. Marinello[7] and G. Francini[1]

[1]Medical Oncology Division, Nuovo Policlinico Le Scotte, University of Siena; [2]Institute of General Surgery, Nuovo Policlinico Le Scotte, University of Siena; [3]Cardiology Division, Nuovo Policlinico Le Scotte, University of Siena; [4]Gastroenteric Surgery, Nuovo Policlinico Le Scotte, University of Siena; [5]Institute of Clinical Surgery, Nuovo Policlinico Le Scotte, University of Siena; [6]Misericordia Hospital, USL 28, Grosseto; and [7]Institute of Biochemistry and of Enzymology, University of Siena, Italy

This randomised clinical trial, involving patients with advanced colorectal cancer, was carried out to compare the effectiveness of accelerated folinic acid (FA) plus 5-fluorouracil (5-FU) with that of the conventional regimen of 5-FU alone. Both regimens were administered with simultaneous supportive care. 185 patients were eligible: 94 were randomly allocated to receive FA 200 mg/m² i.v. plus 5-FU 400 mg/m² i.v. on days 1–5 every 3 weeks; and 91 to receive 5-FU 400 mg/m² i.v. on days 1–5 every 4 weeks. The response rate was 33.3% in the accelerated FA/5-FU and 18.6% in the 5-FU arm ($P = 0.045$). Median survival was 13.5 months in the FA/5-FU arm and 7.5 months in the 5-FU arm ($P = 0.039$). Toxicity was mild and slightly more pronounced in the FA/5-FU arm ($P = 0.078$). This study indicates that, in patients with advanced colorectal cancer, accelerated chemotherapy with FA and 5-FU and simultaneous supportive care is capable of achieving a higher response rate and longer survival than conventional 5-FU alone, without severe toxicity.
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INTRODUCTION

COLORECTAL CARCINOMA is a known chemoresistant neoplasia. The most significant results in the treatment of advanced disease have been obtained using 5-fluorouracil (5-FU) alone or in combination with other drugs, although objective tumour response rates are unsatisfactory and the response duration is short [1].

Pharmacological studies have demonstrated that the action of 5-FU is potentiated by excess intracellular folates, and some studies have reported a slight advantage in favour of folinic acid (FA) with 5-FU over 5-FU alone [2, 3]. It is known that an increase in dose intensity (achieved by increasing the dose of the administered drug or using an accelerated therapy) can lead to a considerable improvement in response rates even in chemoresistant tumors such as colon cancer [4, 5].

Given that the results of our preliminary study of an accelerated FA and 5-FU regimen were interesting in terms of the response rate and the relief of symptoms [6], we began a randomised study to verify the advantage of accelerated FA/5-FU over the conventional regimen of 5-FU alone, when used with simultaneous supportive care potentially capable of reducing chemotherapy-induced side-effects.

PATIENTS AND METHODS

Study design and treatment

Assuming a baseline response rate for 5-FU of 10–15%, a total of 180 patients was considered sufficient to demonstrate a difference in the response rate of 0.20 with a significance level of 0.05 and a power of 0.80 (two-sided test). The primary endpoints were response rate and survival.

The eligibility criteria were a proven diagnosis of advanced

Correspondence to G. Francini at Cattedra di Oncologia Medica, Università di Siena, Nuovo Policlinico Le Scotte, Viale Bracci 11, 53100 Siena, Italy.
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colorectal cancer, measurable or evaluable disease, an age < 72 years, an ECOG performance status ≤3, life expectancy > 2 months, bilirubin < 2 mg/dl, creatinine < 1.5 mg/dl, leukocyte count > 4000/mm^3, platelets > 125 000/mm^3, normal cardiac function, no previous systemic therapy for advanced disease, adjuvant chemotherapy stopped at least 1 year before entering the study. Any prior radiotherapy had to have been discontinued at least 4 weeks before entry. Bone metastases were considered evaluable disease.

The patients were randomised by means of a simple central randomisation list, and not stratified for the main prognostic factors. Screening took place at the different departments involved; the patients were randomised and treated at our Medical Oncology Division.

The study was approved by the Ethics Committee of our Institute and informed oral consent was obtained from each patient or family.

Chemotherapy consisted of FA 200 mg/m^2 i.v. and 5-FU 400 mg/m^2 i.v. for 5 days every 3 weeks in the accelerated arm, and 5-FU 400 mg/m^2 i.v. for 5 days every 4 weeks in the 5-FU arm.

Treatment was planned for 12 cycles or until disease progression; those patients who achieved complete remission received three further "consolidation" cycles. Supportive care consisted mainly of hydration and the administration of agents known to play an important role in the production of cellular energy (such as carnitine derivatives), agents with an antidepressant action (such as S-adenosyl-L-methionine) and those fundamental to nutrition (such as vitamin C). Consequently, 3 days before, during and 5 days after chemotherapy, all patients received 1000 ml of normal saline solution i.v. plus 1 g of vitamin C, 20 mg of carnitine derivatives and 200 mg of ademethionine. Nystatin 10^4 U, and spore suspensions of *Bacillus subtilis* 4×10^9 U were administered daily orally. Conventional oral antidiarrhoea drugs, such as loperamide 2–6 mg, were used for severe diarrhoea, and faecal softening aperients in the case of constipation. Smooth muscle relaxant drugs such as hyoscine were given for intestinal colic, and oral morphine for other abdominal pains.

Response assessment

Response was measured in accordance with the standard response criteria of the Eastern Cooperative Oncology Group [7]. Physical examination, performance status and weight, as well as blood counts and chemistry, were repeated at each cycle. The baseline investigations, including chest X-rays and liver ultrasonography, were repeated at 3-monthly intervals. Abdominal and/or liver computed tomography was repeated at 6-monthly intervals.

Toxicity was evaluated every week by means of the World Health Organization (WHO) 5-point scale. Treatment was postponed for 1 or 2 weeks if grade 2–3 stomatitis, diarrhoea or leucopenia developed; if these side-effects were persistent, chemotherapy was stopped.

Cardiotoxicity was evaluated every 3 cycles by means of electrocardiography and the pre-ejection period/left ventricular ejection time (PEP/LVET).

Statistics

The response rates and grade 2–4 toxicities were compared using the chi-squared test, which was also used to investigate the relationship between baseline variables and therapeutic response. Survival curves were determined by the Kaplan–Meier method and further comparisons were based on the log-rank statistical procedure.

RESULTS

Between the start of 1985 and the end of 1990, a total of 234 patients were screened for the study. 185 patients were eligible: 94 were randomised to the accelerated FA/5-FU and 91 to the 5-FU arm (Table 1). Of these 185 patients, 159 had measurable disease and 26 (9 with bone metastases) evaluable disease.

Of the colon cancer patients, 23 (14 in the FA/5-FU arm and 9 in the 5-FU arm) had received adjuvant chemotherapy: 19 patients with rectal cancer had received adjuvant radiotherapy, 5 of whom had also received chemotherapy. None of the other patients had previously received either chemo- or radiotherapy. 53 patients presented with locally advanced disease; 32 had a surgically unextirpable tumour and 21 had relapsed after radical resection.

The FA/5-FU group received a median of 8.5 cycles of chemotherapy; the 5-FU group a median of 7.0 cycles. The average administered dose intensity was FA 305 mg/m^2/week and 5-FU 610 mg/m^2/week in the FA/5-FU, and 5-FU 368.5 mg/m^2/week in the 5-FU group.

A total of 167 patients (81 receiving FA/5-FU and 86 5-FU) were evaluable. 18 patients (13 on FA/5-FU, 5 on 5-FU) were not considered evaluable for response and toxicity because of protocol violations (n = 7), patient refusal (n = 3), early death due to tumour (n = 1) or because they were lost to follow-up (n = 7) during the first 3 cycles.

The overall response rate was 33.3% (95% confidence limits: 23–43%) for the FA/5-FU patients and 18.6% (95% confidence limits: 10–27%) for those who received only 5-FU. This difference was statistically significant (P = 0.045).

In the FA/5-FU group, 4 patients achieved complete remission (3 with liver metastases and 1 with lung metastases) and 23 achieved partial remission; 35 patients had stable disease and 19 progressive disease. In the 5-FU group, 3 patients achieved complete remission (all with liver metastases) and 13 achieved partial remission; 41 patients had stable disease and 29 progressive disease.

Table 1. *Main characteristics of enrolled patients*

Total cases: 185	FA/5-FU	5-FU
Enrolled patients	94	91
Evaluable patients	81	86
Median age (range)	59 (47–70)	55 (41–72)
Performance status (ECOG):		
1–2	41	48
3	53	43
Adjuvant FA + 5-FU	14	9
Primary		
Colon	58	60
Rectum	36	31
Only one metastatic site	45	52
Predominant metastatic site		
Liver	35	39
Abdomen	29	24
Lung	24	22
Bladder	1	2
Bone	5	4
Measurable disease	83	76
Evaluable disease	11	15
Symptomatic patients	78	74

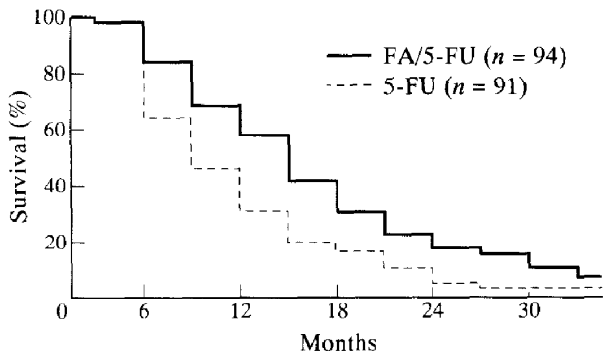

Figure 1. Survival in the two groups of patients with advanced colorectal cancer receiving FA/5-FU (n = 94) or 5-FU (n = 91).

Table 2. Relationship between survival and prognostic factors

	FA/5-FU	5-FU
Performance status		
≤ 2	19.5	11
> 2	7.5*	5*
Disease extent		
Locally advanced	7.5*	5.5*
Distant	17.5	11
Liver involvement		
Limited	21	13
Massive	6.5*	4.5*

*$P > 0.01$

The median response duration was 9 months (2–14) in the FA/5-FU and 5.5 months (2–11) in the 5-FU group (P = 0.08).

At the time of analysis, all of the patients had died. A total of 13 patients were lost to follow-up (5 in the FA/5-FU and 8 in the 5-FU group); all of these patients were considered in the survival analysis. The median survival was 13.5 months (range 3.0–44) in the FA/5-FU and 7.5 months (range 2.5–32) in the 5-FU group; this difference was significant (P = 0.039) (Figure 1).

There was no significant relationship between objective response and primary tumour location (colon versus rectum), major metastatic site or ECOG performance status in either treatment group. Survival was significantly lower in patients with a performance status > 2 ($P < 0.01$), in those with locally advanced disease ($P < 0.01$), and in patients with massive rather than limited liver involvement ($P < 0.01$) (Table 2).

Toxicity

The results concerning toxicity are summarised in Table 3. The side-effects of the treatments were mild and slightly more pronounced in the FA/5-FU than in the 5-FU arm (P = 0.078). The main side-effects were stomatitis and diarrhoea. Post-administration chemical phlebitis in the infusion vein was observed in 46 patients in the FA/5-FU group and 41 in the 5-FU group, but it did not require the suspension of treatment. One patient in the FA/5-FU and 2 in the 5-FU group discontinued treatment after the first 3 cycles because of severe mucositis and desquamation from 5-FU, and 1 patient also reported a hand–foot syndrome. Treatment had to be delayed for 1 to 2 weeks in 12 FA/5-FU and 8 5-FU group patients. The delays were required because of diarrhoea associated with mucositis and/or neutropenia. In 8 FA/5-FU and 5 5-FU patients, the severity of these side-effects required the discontinuation or modification of treatment. No significant cardiotoxicity was observed and, in the majority of cases, there was only low grade nausea, vomiting, leukopenia, dermatosis and alopecia. There were no toxic or septic deaths.

Table 3. The worst WHO grade toxicity in 167 evaluable patients with advanced colorectal cancer

	FA/5-FU (n = 81)				5-FU (n = 86)			
WHO grade	1	2	3	4	1	2	3	4
Stomatitis	18	10	8	3	15	10	5	2
Diarrhoea	12	7	6	3	9	5	4	1
Nausea and vomiting	3	2	2	0	4	1	1	0
Dermatosis	5	3	2	2	3	2	1	1
Leukopenia	5	3	3	0	3	2	2	0

DISCUSSION

In advanced colorectal cancer, the advantage of FA with 5-FU over 5-FU alone seems to have been established in terms of tumour response rate, but only a few trials have been able to demonstrate any advantage in terms of survival [8–13].

The lack of any clear advantage in survival may be because the low intensity of the administered 5-FU dose leads to only small differences in the rate and median duration of tumour response [9, 11].

In the present study, the FA/5-FU schedule was administered for 5 days every 3 weeks in order to increase dose intensity, and led to a response rate of 33.3% (versus 18.6% with the conventional 5-FU regimen). Although higher response rates have been reported in other randomised studies, we consider 33.3% to be high; furthermore, we also observed a high rate of stabilisation which, together with the satisfactory objective response, can be considered a beneficial effect of treatment.

The median duration of response was better in the FA/5-FU patients than in those on 5-FU (9.0 months versus 5.5 months), and was followed by a better median survival (13.5 months versus 7.5 months) (P = 0.039). The median survival in the 5-FU arm (7.5 months) was relatively short, but similar to that reported in other trials [11, 14], and it may be explained by the high proportion of patients with a performance status of 3. In agreement with other studies, a low performance status, surgically inextirpable tumour or abdominal relapse and the extension of liver involvement were all found to be negative prognostic factors for survival in both treatment arms [15].

The consistent advantage of the combined FA/5-FU treatment schedule over the conventional schedule of 5-FU alone may be due to the high average dose intensities of both FA and 5-FU. Most of the published randomised studies have used the conventional schedule of FA/5-FU every 4 weeks, with an initial 5-FU dose intensity of between 460 and 500 mg/m^2/week and an initial FA dose intensity of approximately 250 mg/m^2/week, but overall survival has rarely significantly improved [5, 10, 11, 16].

The delivered dose intensity of 610 mg/m^2/week of 5-FU and 305 mg/m^2/week of FA used in the FA/5-FU arm of the present study is considerably higher than that found in many other trials. Nevertheless, the fact that the dosing of 5-FU was accelerated in the FA/5-FU arm but not in the unmodulated 5-FU arm introduces two confounding factors into the analysis (the effects of FA modulation and the increased dose intensity of 5-FU), and so the statistically significant difference in survival between the

two treatment arms may be related to the addition of leucovorin, rather than to the shortening of the cycle length.

It is well known that FA/5-FU chemotherapy can cause side-effects such as nausea, vomiting and diarrhoea, particularly when it is infused on 5 consecutive days and if the intensity of the 5-FU dose is increased. In this study, the side-effects mainly consisted of mild stomatitis and diarrhoea, which appeared to be slightly more pronounced in the accelerated FA/5-FU arm. However, although the difference between the two groups was of borderline significance ($P = 0.078$), the incidence of FA/5-FU toxicity was lower than that usually reported in other trials; furthermore, the diarrhoea was rarely severe and regressed rapidly with supportive care. Very few patients (12 in the FA/5-FU group and 8 in the 5-FU group) required any delay or modification in their treatment schedule. We therefore believe that the administration of supportive care (mainly based on ensuring persistent hydration) was useful in preventing or reducing chemotherapeutic toxicity.

In conclusion, our study indicates that, in patients with advanced colorectal cancer, accelerated chemotherapy with FA and 5-FU and simultaneous supportive care is capable of achieving a higher response rate and longer survival than the conventional 5-FU alone without severe toxicity. In addition, given that there is still no unanimous consensus as to the best schedule to adopt in cases of advanced disease, we fell that our results may also contribute towards clarifying the question.

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