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Double Modulation of 5-Fluorouracil in Advanced Colorectal Cancer With Low-dose Interferon-α2b and Folinic Acid. The "GISCAD" Experience

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In advanced colorectal cancer the addition of folinic acid (FA) has been shown to lead to increased activity, at least in terms of response rate, in comparison with 5-fluorouracil (5FU) alone. Similarly, interferon-α (IFN) is able to potentiate 5FU, although high doses cause heavy toxicity. Given the different mechanisms of action of the two agents, the double modulation of 5FU deserves clinical evaluation. In a multicenter study (involving both primary care and referral institutions) 63 patients with advanced colorectal cancer, previously untreated with chemotherapy, received, in an outpatient setting, FA (200 mg/m² i.v. bolus) + 5FU (400 mg/m² i.v. in 15 min) for 5 consecutive days every 4 weeks + IFN 3 × 10⁶ U on alternate days, starting 1 week before chemotherapy. During the 5 days of 5FU + FA, IFN was administered daily. The antitumour activity, the impact on response duration and survival and toxicity of the combination were evaluated according to WHO criteria. Of the 63 enrolled patients, 56 were evaluable: there were 2 complete responses (3%) and 13 partial responses (21%), giving an objective response rate of 24% (95% confidence interval 13–35%); no change was observed in 17 cases and progressive disease in 24. Median duration of response was 9 months and median survival (all patients) 13 months. Toxicity was acceptable, even though 4 patients presented reversible grade 4 side-effects (2 mucositis and 2 diarrhoea). With this schedule and these doses, addition of IFN did not lead to any increase in the activity of 5FU + FA. In colorectal cancer, further clinical studies with these drugs should be based on a deeper experimental knowledge of their mechanisms of interaction.

Keywords: 5-fluorouracil, interferon-α2b, folinic acid, colorectal cancer
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INTRODUCTION

THE BIOCHEMICAL modulation of 5-fluorouracil (5FU) with folinic acid (FA) led to the most significant advance in the systemic chemotherapy of metastatic colorectal cancer of the last decade. A recent meta-analysis of nine phase III published trials [1], including a GISCAD study [2], has confirmed the clear advantage of the combination over 5FU alone in terms of objective response rate, although overall survival is no longer than with 5FU alone.

The possibility that the activity of 5FU might be improved by the addition of interferon-α (IFN) was suggested by experimental observations [3] of a decrease in thymidine kinase activity, with a reduction in the rate of phosphorylation of thymidine and consequent inhibition of thymidine incorporation into DNA. Pharmacokinetic studies showed a decrease in 5FU clearance (and an increase in the 5FU area under the curve) when the drug was administered concomitantly with IFN [4]. Furthermore, the induction of thymidylate synthase (TS) associated with fluoropyrimidine exposure (which can be an important mechanism of cell resistance) can be eliminated by IFN [5]. In the

clinical field, Wadler [6], reported 63% partial responses (PR) in previously untreated patients who were given high doses of IFN (9×10^6 U three times a week), although there were important side-effects (mucositis, diarrhoea, fever and neurotoxicity), and three toxic deaths.

Clinical data have suggested that an optimal potentiation of 5FU can also be achieved using relatively low doses of IFN [7] which can be, obviously, less toxic and better tolerated. In order to maximise this potentiation, IFN should also be administered before 5FU: Elias [8], in MCA-38 and HL-60 cell lines, observed a schedule-dependency of the modulation of 5FU with IFN, the best sequence being IFN followed by 5FU.

Given that both FA and IFN are capable of increasing the activity of 5FU, it was felt that a regimen including all three drugs (and thus providing a double modulation of 5FU) might be of interest in advanced colorectal cancer. In order to evaluate the combination, the present phase II trial was conducted by GISCAD (Italian Group for the Study of Digestive Tract Cancer).

MATERIALS AND METHODS

Between December 1990 and November 1991, 63 consecutive advanced colorectal cancer patients, previously untreated with chemotherapy, entered the study. The eligibility criteria were the presence of measurable disease, age <70 years, ECOG performance status (PS) ≤2, life expectancy >3 months, adequate bone marrow reserve, no renal or hepatic failure and no ischaemic cardiopathy. Patients with resectable liver or lung metastases were excluded from the study, as were those with brain metastases. Radiotherapy was allowed only if a site other than those measurable for the study was irradiated. The characteristics of the patients, all of whom gave their oral informed consent, are described in Table 1.

Table 1. Main characteristics of treated patients

Total number	63
Males/females	48/15
Mean age in years (range)	58.7 (35–70)
Performance status	
0	2
1	54
2	7
Primary site	
Colon	46
Rectum	16
Multiple	1
Site of metastases	
Liver only	26
Lung only	5
Pelvis	3
Abdomen	2
Others	4
Multiple (including liver)	17
Multiple (without liver)	6

The drug schedule was as follows: FA (200 mg/m^2 i.v. bolus), immediately followed by 5FU (400 mg/m^2 i.v. dissolved in 100 ml 5% glucose, given over 15 min) for 5 consecutive days every 4 weeks. Continuous treatment with subcutaneous IFN-α2b was started the week before the beginning of 5FU + FA at a dose of 3×10^6 U on alternate days (except during the 5 days of FA + 5FU, when it was administered daily at the same dose). Oral paracetamol (500 mg × 3) was administered together with IFN.

Every three courses, objective response (OR) was assessed by means of imaging techniques (ultrasonography, computed tomography scan, chest X-ray) and classified according to WHO criteria [9].

Chemotherapy was planned for a maximum of six courses in patients with a complete response (CR), and 12 courses in those with partial response (PR) or no change (NC): after this period, a careful follow-up was programmed. The treatment was discontinued in the case of disease progression. No second-line chemotherapy was foreseen.

Before each course, white blood cells and platelet counts, liver and renal function tests and tumour markers were assessed.

Toxicity was evaluated according to WHO criteria. In case of grade 1 leucopenia or thrombocytopenia, therapy was interrupted until normalisation. If the same parameters were evaluated as grade 2, treatment was interrupted until normalisation and then 75% of the 5FU dose was administered. The dose was 50 % in the case of grade 3 myelosuppression. If grade 2 and 3 mucositis or diarrhoea occurred, treatment was stopped until normalisation and then 50% of the 5FU dose was given. In the case of good tolerance at this dose level, the following cycles were performed with an increase of 100 mg/m^2/every course until the initial dose was reached. On the contrary, if tolerance was poor, the 5FU dose was reduced to 25% of the initial one. IFN doses were reduced to 50% in the case of grade 3 fever or hepatotoxicity (transaminases: 5–10 × normal values). No reduction of FA doses was adopted. For all grade 4 toxicity permanent discontinuation of treatment was planned.

The sample size was established according to Simon's two-stage optimal design [10]: P0 and P1 were set at 20 and 40% and, with α error of 0.05 and β error of 0.10, the combination had to be rejected if four or fewer responses were observed among the first 19 patients or if 15 or fewer responses were observed in 54 patients.

Survival and the duration of response were calculated from the beginning of therapy. Overall survival was established using the Kaplan–Meier method [11].

RESULTS

The number of treated patients is slightly higher than the number foreseen, because the multi-institutional character of the study implied the possibility of enrolling approximately 10% unevaluable subjects.

Of the 63 patients admitted to the study, 7 were not evaluable for OR: 5 were lost to follow-up and in the remaining 2 chemotherapy was discontinued after one course because of toxicity (ischaemic cardiopathy and refusal of the patient to

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Table 2. Toxicity

	Patients' grade			
	1	2	3	4
Nausea and/or vomiting	17	6	1	—
Diarrhoea	8	24	3	2
Stomatitis	12	18	5	2
Leucopenia	5	8	—	—
Thrombocytopenia	2	2	—	—
Anaemia	—	2	—	—
Alopecia	4	2	—	—
Rash	4	1	—	—
Cardiotoxicity	—	1	—	—
Neurotoxicity	—	—	—	—

Flu-like symptoms with fever were observed in 22 patients, fatigue in 16 and conjunctivitis in 2 patients.

continue treatment in 1 case and grade 4 diarrhoea in the other). However, all of these 7 cases were considered as chemotherapy failures and maintained in the denominator of the fraction expressing the clinical activity of the treatment. Patients received a median of five courses (range one to 12) and the total number of administered courses was 309. The delivered dose intensity of 5FU was 450 mg/m^2/week, 90% of the programmed one.

As far as the objective responses are concerned, two CR (3%) and 13 PR (21%) were observed, with an overall response rate of 24% (95% confidence interval 13–35%). Transient lesion stabilisation (NC) occurred in 17 patients (27%) and disease progression (PD) during treatment was observed in 24 patients. Both CRs concerned patients with liver metastases. The 13 PRs included cases with liver (4), multiple sites (3), lung (2), pelvis (2), supraclavicular lymphnode (1) and abdomen (1) involvement. None of the initial clinical parameters (reported in Table 1), with the exception of PS influenced the response rate. In fact, the presence of 11% of the patients in PS 2, with only 1 PR, may have slightly reduced the global activity of the regimen. As far as the site of metastases was concerned, an apparently better response was showed by patients with only lung or pelvis involvement, but the numbers are too small to permit any conclusion.

The median duration of CR + PR was 9 months (range 4–19+), with a slight advantage for CR versus PR (10.5 and 9 months, respectively). Median survival time for all patients was 13 months (range 1–28+); all of the non-responders died of their disease within a few months of the start of treatment.

Toxicity was present in most of the patients (Table 2), including 4 cases of reversible grade 4 side-effects (2 mucositis and 2 diarrhoea). Some of the symptoms (fever and fatigue) were attributable to IFN, although there were no cases of neurotoxicity. The incidence and importance of classic FA+5FU toxicities (stomatitis and diarrhoea) were similar to those observed in previous studies by us and others with these two drugs alone. It is noteworthy that the modulation of 5FU dosage we adopted allowed the administration of a high dose intensity of the drug and that in no case did the side-effects due to IFN cause a reduction in this agent's dosage.

DISCUSSION

After the experimental demonstration that high-dose IFN is able to increase the activity of 5FU, several studies have been carried out in order to evaluate the role of this association in the clinical setting. The exciting results reported by Wadler in 1989/1990 were not completely confirmed by other authors [12, 13], although an ECOG study [14] supported the data of the prior trial (response rate not significantly different, 42 versus 63%, and confidence intervals overlapping, with less side-effects): the response rate fell from 63 to 30–40% and severe toxicity was confirmed. Thus, the therapeutic index of this combination appeared lower than expected. Moreover, the final reports of two large phase III trials, recently presented, did not show any advantage for 5FU + IFN versus 5FU alone [15] or 5FU + FA [16], even though it should be noted that IFN appeared able to modulate 5FU similarly to FA with a lower incidence of gastrointestinal toxicity.

In vitro and *in vivo* colon cancer xenograft studies support the enhanced activity of the 5FU/FA combination induced by IFN [17, 18] and, on the basis of this evidence, several studies have been carried out in order to evaluate the clinical activity of the double biochemical modulation of 5FU.

At least two of these clinical trials have indicated the feasibility and activity of double modulation. Using 5FU 370–425 mg/m^2 + FA 500 mg/m^2 (from days 2 to 6) and IFN 5 × 10^6 U from days 1 to 7, recycled every 28 days if toxicity had resolved, Grem and colleagues [19] obtained a 44.4% response rate in 18 patients with colorectal cancer not previously treated with 5FU; the time to treatment failure was 6.4 months and median survival had not been reached at the time of publication. These data have been recently confirmed in a larger phase II study conducted at three institutions [20]. Using 5FU and FA from days 2 to 6, at doses of, respectively, 370 and 200 mg/m^2, + IFN 3 × 10^6 U days 1–7 (all drugs recycled every 21 days), Cascinu [21] observed 51% CR + PR (95% confidence interval 37–65%). At the time of publication, all of the CR patients were still in response and the median duration of PR was 10 months. Once again, median survival had not been reached, as 33 out of 45 patients were still alive after a median follow-up of 14 months. Toxicity was acceptable in both of these trials, consisting of grade III mucositis and diarrhoea in no more than 20% of the patients.

However, other studies evaluating 5FU + FA + IFN have failed to demonstrate any advantage from the addition of IFN [22, 23]. A review of the published studies is summarised in Table 3: on the whole, these results do not give a definitive answer to the question about the worth of the double versus single modulation of 5FU. Data from phase III studies are needed.

The present study was based on the clinical and experimental considerations reported above: in particular, after a previous experience with high-dose IFN (10 × 10^6 U three times a week), during which we observed heavy toxicity without any increase in activity [40], we decided to evaluate low doses of the drug. The adopted regimen also included the administration of IFN in the period between the courses of 5FU + FA. This choice was made empirically, on the basis of our own and others' previous experience.

This represents the largest phase II study so far carried out in a population of non-pretreated patients: this is an important point, as most of the published studies also included pretreated patients, who generally do not respond and may be a source of confusion in the evaluation of activity. Furthermore, the number of patients included in our study was large enough to allow the correct evaluation of response rate.

The response rate (24%) we achieved was not better than reported in the recent meta-analysis for FA + 5FU alone.

Table 3. Phase I and II trials of 5FU + FA + IFN in advanced colorectal cancer

Author	Patients (not pretreated)	Schedule (mg/m²)	Response (%)
Schmoll [23]	32	5FU 500–600 FA 200 IFN 5 × 10⁶ U/m²	9.3
Yalavarthi [24]	46	5FU 370 FA 200 Escalated IFN	30
Piedbois [25]	10	5FU 400 FA 200 IFN	70
Taylor [26]	19	5FU 400 FA 250–500 IFN 10 × 10⁶/U 3/week	26
Inoshita [27]	46	5FU 370 FA 200 Escalated IFN	30
Punt [28]	19	5FU 60 every 48 h FA 90 every 6 h × 2 days IFN days 1,3,5 every 2 weeks	26
Seymour [29]	35	5FU 400 FA 200 escalated IFN	52
Sobrero [30]	15	5FU 500/week FA 500/week IFN 3 × 10⁶ U 3 days/week	20
Kreuser [31]	34	5FU 400–750 days 1–7 FA 200 days 1–7 IFN 5 × 10⁶ U days 1–7	35
Bukowski [32]	55	5FU 430 FA 200 IFN 4 × 10⁶ U/m² Days 1–5	27.2
Lembersky [33]	14	5FU 500 (c.i.) × 5 days FA 200 IFN 5 × 10⁶ 3/week	81
Moore [34]	25	5FU 375 FA 200 IFN 3 × 10⁶ U 3–5/week	28
van Hazel [35]	25	5FU 370 FA 200 IFN 10 × 10⁶ U 3/week	28
Pavesi [36]	40	5FU 375 FA 100 IFN-β 3 × 10⁶ U 3/week	40
Dalri [37]	14	5FU 370 FA 200 IFN 9 × 10⁶ U 3/week	57
Dirix [38]	8	5FU 425 FA 20 IFN 5 × 10⁶ U 3/week	62.5
Sinnige [39]	30	5FU 750 days 2–3 FA 60 orally every 8 h days 1–3 IFN 18 × 10⁶ U days 1–3 every 2 weeks	57

Only studies not extensively quoted in the text are reported. Doses of 5FU and FA are for 5 days every 28 when not otherwise specified. c.i., continuous infusion.

Furthermore, neither the duration of response nor the overall survival appeared increased by the addition of IFN. How can this failure be explained?

One reason could be that, in our study, the 5FU dose intensity (DI) (scheduled: 500 mg/m²/week, delivered: 450 mg/m²/week) might be lower than that used by Grem and Cascinu. However, in the former trial, the scheduled DI was 462 mg/m²/week and the delivered one 466 ± 13 mg/m²/week, while in the latter 5FU was scheduled at a DI of 616 mg/m²/week (with a delivered DI of 590 mg/m²/week). It seems unlikely that such a notable

difference in activity can be explained only on the basis of a decrease of no more than 30% in DI. In other studies, DI was not reported.

Another, and probably more pertinent, explanation for the results of our study could lie in the negative interaction among 5FU, FA and IFN as reported by Schuller [41]. FA could reverse the pharmacokinetic effects of IFN on 5FU *in vivo*; while the plasma levels of 5FU are increased in patients receiving IFN, they are similar to those reached with 5FU alone when FA is added to the combination.

In conclusion, it is still difficult to define the optimal schedule of this combination, its real activity and whether it is a step forward in comparison with 5FU + FA.

Until reproducible activity and feasibility of the double modulation of 5FU with these two agents is demonstrated in the clinical setting, its use should be restricted to research studies and any untimely introduction into clinical practice should be avoided.

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Inter-relationships Between Single Carbon Units' Metabolism and Resting Energy Expenditure in Weight-losing Patients with Small Cell Lung Cancer. Effects of Methionine Supply and Chemotherapy

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The one-carbon unit metabolism was investigated in 8 weight-losing patients with small cell carcinoma of the lung (SCLC). At diagnosis, 6 of the 8 patients had elevated formiminoglutamic acid (FIGLU) excretion after a histidine load, suggesting a lack of one-carbon units. In accordance, a significant decrease of FIGLU excretion was observed in the patients after oral administration of DL-methionine for 4 days. The elevated FIGLU excretion was positively correlated to weight loss prior to diagnosis and negatively correlated to serum albumin at time of diagnosis. After 3 months of combination chemotherapy, FIGLU excretion was reduced in all patients except 1, who had progressive disease. Despite the elevated FIGLU excretions, all patients had normal blood folate levels. The resting energy expenditure (REE) was recorded in 7 patients, and a significant, postive correlation was observed between pretreatment FIGLU excretion and REE, although the REE measured in this group of patients was within the normal range. These data demonstrate an increased demand of "active" one-carbon units in energy consumption in a group of weight-losing cancer patients. The one-carbon unit deficit was reconditioned by oral administration of the one-carbon unit donor DL-methionine.

Key words: one-carbon units, energy expenditure, FIGLU excretion, metabolism, methionine, small cell lung cancer

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INTRODUCTION

TO MAINTAIN a stationary body weight, a delicate equilibrium between caloric intake and total energy expenditure must exist. Obviously, this balance deteriorates in cancer cachexia, but the physiological derailments causing the weight loss had been a matter of much debate. Clinical and experimental observations in cancer cachexia have documented both qualitative and quantitative metabolic disturbances. Among these are: (1) elevated resting energy expenditure (REE) [1, 2], (2) diet-induced hyperthermogenesis [3, 4] and (3) changes in the intermediary metabolism of carbohydrates, proteins and lipids [5–11].

Transfer of carbon-1-units involving tetrahydrofolic acid or S-adenosylmethionine plays a crucial role in *de novo* synthesis of basic cell constituents (Figure 1). The conversion of the hydroxyamino acid serine to glycine is quantitatively the most important donor of "active" single carbon units in the human