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Different Dose Regimens of 5-Fluorouracil and Interferon-α in Patients With Metastatic Colorectal Carcinoma

P. Ragnhammar, H. Blomgren, D. Edler, G. Lundell, I. Magnusson and T. Sonnenfeld

Three different 5-fluorouracil (5-FU)–interferon-α-2b (IFN)-containing regimens were designed for treatment of patients with advanced colorectal cancer. 87 patients with a Karnofsky index ≥70 were included in three sequential non-randomised phase II trials. Regimen A consisted of 5-FU (750 mg/m²/day) given as a continuous infusion on days 1–5 followed by weekly 1-h intravenous infusions until week 8. IFN (5 MU) was given subcutaneously on days 1, 3 and 5 followed by injections (9 MU) every second day until week 8. The cycle was then repeated. Regimen B consisted of 5-FU (750 mg/m²/day) given as a continuous infusion on days 1–5 followed by 5-min intravenous injections on days 12 and 19. IFN (3 MU) was given subcutaneously on days 1–5 followed by injections (5 MU) on days 11–13 and 18–20. The cycle was repeated every fourth week. Regimen C consisted of 5-FU (750 mg/m²/day) given as a continuous infusion on days 1–5. IFN (3 MU) was given subcutaneously on days 1–5. The cycle was repeated every third week. The objective response rates (complete response (CR) and partial response (PR)) after approximately 4 months of therapy or longer were as follows: regimen A (n = 27) 22% (2 CR, 4 PR), regimen B (n = 33) 42% (4 CR, 10 PR) and regimen C (n = 27) 22% (1 CR, 5 PR). The corresponding response figures for previously untreated patients were regimen A 50%, regimen B 64% and regimen C 38%. Response durations varied from a few weeks up to 142 + weeks. Toxicities were generally mild and reversible, and the treatments were convenient for the patients and cost effective since the 5-day infusions could be given by a portable pump without hospitalisation. Our results are in agreement with those of others showing that 5-FU/IFN combinations can be highly effective in advanced colorectal cancer, and that a number of factors such as doses, dose intensities, infusion rates and timing of the two drugs may be crucial for the anti-tumour activity of this drug combination.

Key words: colorectal carcinoma, 5-fluorouracil, interferon, therapy
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INTRODUCTION

5-FLUOROURACIL (5-FU), which was discovered by Heidelberg and associates in 1957 [1], is the most effective cytotoxic drug against advanced colorectal cancer (CRC) with response rates usually ranging from 10 to 20% [2]. During recent years, attempts have been made to increase its efficacy by combining it with other agents, modulators, which by themselves exhibit modest or no detectable anti-tumour activity. Interferon-α (IFN) is one such modulator. Its principle mechanism of action is currently uncertain. However, evidence exists that this agent alters the 5-FU plasma pharmacokineties by increasing the area under the concentration–time curve [3, 4], increasing the formation of fluoro-deoxyuridine-monophosphate (FdUMP) [5], inhibiting the 5-FU-induced upregulation of thymidylate synthase (TS) [6], inhibiting upregulation of the thymidine salvage enzyme (thymidine kinase) [7], and enhancing incorporation of fluorodeoxyuridine triphosphate (FdUTP) into DNA [8].

In phase II studies using IFN with 5-FU on a weekly bolus schedule following a 5-day continuous infusion, the tumour response rate has varied from 26 to 63% [9–12]. Inspired by these results, we have designed new 5-FU/IFN schedules with the aim of reducing toxicity and maintaining or possibly further increasing the anti-tumour activity. In this paper, we report on the clinical results of three non-randomised 5-FU/IFN regimens in patients with advanced CRC.

PATIENTS AND METHODS

Eligibility criteria

All patients who had histological proof of metastatic or unresectable CRC, were older than 15 years, had an estimated life expectancy ≥16 weeks, with measurable disease and a Karnofsky index of ≥70 were considered for these trials. They were required to have an adequate renal function (serum creatin-

Correspondence to P. Ragnhammar.
P. Ragnhammar, H. Blomgren and G. Lundell are at the Department of Oncology, Radiumhemmet, Karolinska Hospital; and D. Edler, I. Magnusson and T. Sonnenfeld are at the Department of Surgery, South Hospital, Stockholm, Sweden.
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ine <120 μmol/l; blood urea nitrogen <30 mg/dl), liver transaminases not higher than three times the normal values or five times in patients with extensive liver metastases, bilirubin <22 μmol/l and an albumin value >37 g/l. Moreover, haematological parameters had to be as follows: leucocyte count $>4.0 \times 10^{-9}$ l; granulocytes $>1.8 \times 10^{-9}$ l; platelets $>150 \times 10^{-9}$ l, and haemoglobin >100 g/l. Patients with active cardiac disease, infection, brain metastases, hypercalcaemia or those who had undergone surgery, chemo-, immuno- or radiation therapy within the last 4 weeks were not eligible.

Study design

In the 4 weeks before entering the trials, the sizes of the metastatic lesions were determined by computed tomography (CT) scan and/or plain X-ray examinations, and the serum levels of the tumour markers' carcinoembryonic antigen (CEA), CA50 and CA19–9 were determined. Size of the lesions was determined every second (regimen A) or fourth treatment cycle (regimens B and C). Tumour marker determinations were performed after each cycle. Treatment was discontinued in patients showing progressive disease. Recombinant IFN-α was used (Intron A (alpha-2b), Schering-Plough, Kenilworth, New Jersey, U.S.A.).

Regimen A

5-FU, 750 mg/m^2/day, was administered as a continuous infusion intravenously (i.v.) for the first 5 days followed by weekly 1-h infusions of 750 mg/m^2 for 6 weeks starting on day 12. IFN (5 MU) was given subcutaneously (s.c.) on days 1, 3 and 5 and then every second day (9 MU) until week 8. The cycle was repeated after 8 weeks.

Regimen B

5-FU, 750 mg/m^2/day, was administered as a continuous infusion i.v. during the first 5 days followed by 5-min bolus injection of 750 mg/m^2 on days 12 and 19. IFN (3 MU) was given s.c. on days 1–5 and then (5 MU) on days 11–13 and 18–20. The cycle was repeated every fourth week.

Regimen C

5-FU, 750 mg/m^2/day, was administered as a continuous infusion i.v. for 5 days. IFN (3 MU) was given s.c. on days 1–5. The cycle was repeated every third week.

In some patients, the intervals between the treatment cycles were delayed by 1–3 weeks due to toxicity (see below), but the doses of 5-FU and IFN were kept constant.

Serum tumour markers

CEA and CA19–9 in serum were measured using the Abbott IMx Automated Benchtop Immunochemistry Analyser System (Chicago, U.S.A.) [13]. CA 50 was measured using a two-step immunoradiometric assay (IRMA) from Behring (Marburg, Germany) [14].

Toxicity criteria

Toxicity was graded according to the criteria of the World Health Organisation [15].

Response criteria

Complete response (CR): disappearance of all visible tumour disease and normalisation of tumour markers (CEA, CA19.9 and CA50). Partial response (PR): more than 50% reduction of the sum of the products of the longest perpendicular diameters of all lesions without appearance of any new metastases. Stable disease (SD): no greater than 25% increases of the size of any lesion without appearance of any new metastases. Progressive disease (PD): one or more tumour lesions increased in size by >25%.

The duration of response had to last for at least 4 weeks in order to be classified as a response (CR and PR).

RESULTS

Demographic and clinical characteristics

87 consecutive patients were enrolled in these trials (Table 1). There were 47 males and 40 females with an age range of 22–80 years. All patients were primarily treated surgically. Thirty-four per cent of the patients had received immunotherapy, chemotherapy or radiation therapy for advanced disease and 2% had received adjuvant chemotherapy. The majority of the metastatic lesions were observed in the liver and lungs. There were no significant differences between the patients of the treatment regimens with regard to age, site of metastases, degree of differentiation of the tumour, stage and median time from surgery to start of therapy.

Response to therapy

As shown in Table 2, all treatment regimens yielded both complete and partial tumour responses. The highest objective response rate, 42% (95% confidence interval (CI) 28–61%), was noted for regimen B. For regimens A and C, the response rate was 22% (95% CI 5–36%). The corresponding figures for previously untreated patients were 50% for regimen A, 64% for regimen B and 38% for regimen C (Table 3). All responses were noted at the first evaluation, i.e. after two cycles for regimen A and four cycles for regimens B and C. Tumour sites of the responding patients as well as response durations are listed in Table 4. There did not seem to be any association between the duration of the response (5–142+ weeks) and the site of the responding lesion.

Toxicity

The side-effects reported for each patient during the entire treatment periods are listed in Table 5. The average time of treatment using regimen A was 168 days (range 112–336), regimen B 196 days (range 112–588) and regimen C 168 days (range 84–462). The median numbers of treatment courses were: regimen A 3 (range 2–6), regimen B 7 (range 4–21) and regimen C 8 (range 4–22).

Toxicity profiles differed somewhat between the three treatment regimens. Fatigue was noted in 81% of the patients in group A, but only in 30 and 22% in groups B and C, respectively. Alternatively, hair loss was less common in group A. Diarrhoea seemed to be more common in groups A and C than in group B, and nausea/vomiting was not noted in group C. Treatment-induced fever, stomatitis and leucopenia did not seem to differ between the groups. The side-effects were usually readily reversible, but 2 patients required hospitalisation for management of toxic side-effects (group A: dyspnoea; group B: stomatitis). No treatment-related deaths occurred.

DISCUSSION

After publication of the results of Wadler and associates [9, 10, 16], reporting an objective response rate of 76 and 63% in patients with previously untreated metastatic CRC, several phase II studies were published using the same or slightly modified 5-FU/IFN-α regimens [11, 17–24]. Although the effectiveness of this regimen was confirmed, none of the reports confirmed the high remission rate reported by Wadler and

Table 1. Patients' characteristics

	Treatment regimen		
	A (n = 27)	B (n = 33)	C (n = 27)
Sex			
Male	14	20	13
Female	13	13	14
Age (years)			
Median	55	60	61
Range	22–75	27–73	35–80
Performance status (Karnofsky index)			
Median (%)	80	90	90
Range	70–100	80–100	80–100
Pretreatment			
Radiotherapy	—	2	2
Chemotherapy	—	4	7
Immunotherapy	15	5	2
None	12	22	16
Site of primary tumour			
Colon	16	18	15
Rectum	11	15	12
Site of metastases*			
Liver	12	15	15
Lungs	10	7	1
Lymph nodes	9	12	4
Perineum/pelvis	3	—	—
Abdominal wall	2	—	2
Abdominal cavity	4	2	4
Skeleton	—	1	1
Other	2	2	1

* Each patient could have metastases to several sites.

Table 2. Response to therapy

Regimen	CR (%)	PR (%)	SD (%)	PD* (%)
A (n = 27)	2 (7)	4 (15)	5 (19)	16 (59)
B (n = 33)	4 (12)	10 (30)	5 (15)	14 (43)
C (n = 27)	1 (4)	5 (19)	6 (22)	15 (55)

Number of patients in each response category is shown. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. * Determined after two treatment cycles of regimen A and four cycles of regimens B and C. Values refer to numbers of patients.

Table 3. Objective responses in previously untreated patients

Regimen	PR + CR (%)	Response duration (weeks) Median	Range
A (n = 12)	50	22	5–142
B (n = 22)	64	25	4–90
C (n = 16)	38	42	24–56

Determined after two treatment cycles of regimen A and four cycles of regimens B and C.

associates [9, 10, 16]. The median objective response rate in these studies is 37%, with a range of 32–42%. Two prospective randomised trials in patients with advanced CRC have also been initiated in order to determine the possible benefit by adding IFN to 5-FU. In one, the control arm received a continuous 5-day infusion of 5-FU followed by weekly bolus injections. The experimental arm received, in addition to this 5-FU schedule, 9 MU of IFN-α three times a week. The response rates (19 and 31%, respectively) and survival did not differ significantly between the two groups [25]. Similarly, negative results have been reported by Cellerino and associates [26]. The two treatment arms received identical 5-FU schedules: bolus injections on five consecutive days followed by weekly injections, without or with 3 MU of IFN-α.

The aim of the present study was to further examine the effectiveness of combinations of 5-FU and IFN in the treatment of advanced CRC. Three different regimens were designed. All started with a loading dose of 5-FU given as a continuous infusion for 5 days followed by bolus injections or infusions of a short duration (regimens A and B). Although several trials have shown that the anti-tumour activity of continuous infusions of 5-FU is more effective (response rates of 30–54%) than bolus injections (response rate of approximately 10%) [27–34], we used both types of administration. One reason for this is that there is circumstantial evidence that the mechanisms of 5-FU action might be dependent on the exposure time of tumour cells to the drug. This is exemplified by the fact that the cytotoxic

Table 4. Characteristics of responding patients

Age	Sex	Primary tumour	Site/ response	Overall response	Duration (weeks)	Survival (weeks)
Regimen A						
55	M	Rectum	Lung/CR	CR	5	26
49	F	Colon	Skeleton/PR	PR	26	55
61	F	Colon	LN/PR	PR	142+	125+
61	F	Rectum	Lung/PR	PR	35	62
35	M	Appendix	Abd.cav./CR	CR	17	82
22	F	Colon	Liver/PR	PR	6	25
Regimen B						
49	F	Colon	LN/CR	CR	24	53
40	M	Rectum	Lung/CR P.mass/PR	PR	80+	97+
65	F	Colon	Lung/PR	PR	26	90
61	M	Colon	LN/CR	CR	13	38+
67	F	Rectum	Liver/PR	PR	24	79
57	M	Rectum	Liver/CR	CR	65+	78+
62	M	Colon	Liver/PR	PR	22	39
63	F	Colon	Lung/CR	PR	61+	78+
58	M	Rectum	Liver/PR	PR	21+	38+
55	F	Colon	P. mass/PR	PR	90+	108+
50	M	Rectum	Liver/PR	PR	9+	26+
52	M	Rectum	Liver/PR	PR	4+	21+
30	F	Colon	LN/CR	CR	34+	51+
26	F	Colon	Lung/PR	PR	52	78+
Regimen C						
64	M	Colon	Liver/CR	CR	51+	68+
71	F	Colon	Abd.cav./PR	PR	24+	41+
69	F	Rectum	P.mass/PR	PR	56+	73+
61	F	Rectum	LN/PR	PR	38+	55+
80	F	Rectum	LN/CR Liver/PR	PR	46+	63+
55	F	Colon	Liver/PR	PR	27+	63+

LN, lymph nodes; Abd. cav., abdominal cavity; P. mass, pelvic mass; M, male; F, female.

Table 5. Toxicity grades

	Regimen A (n = 27)					Regimen B (n = 33)					Regimen C (n = 27)				
	I	II	III	IV	(%)	I	II	III	IV	(%)	I	II	III	IV	(%)
Fatigue	18	3	1	0	81	5	5	0	0	30	0	6	0	0	22
Fever	2	9	0	0	41	3	14	0	0	52	4	9	0	0	48
Stomatitis	9	2	0	0	41	8	2	1	1	36	7	2	0	0	33
Leucopenia	0	7	3	0	37	7	4	1	0	36	3	4	0	0	26
Diarrhoea	6	3	0	0	33	1	2	0	0	9	6	3	0	0	33
Nausea/vomiting	5	3	0	0	30	2	2	2	0	18	0	0	0	0	0
Hair loss	0	2	1	0	11	2	5	1	0	24	0	5	2	0	26
Dyspnoea	0	2	1	0	11	0	0	0	0	0	0	0	0	0	0
Neurotoxicity	0	0	2	0	7	0	0	0	0	0	0	0	0	0	0
Hand–foot syndrome	0	0	0	0	0	2	4	0	0	17	0	0	0	0	0

effect of 5-FU for tumour cells *in vitro* is greatly increased by folinic acid when the cells are exposed to low concentrations of the drug for 72 h, but there is only minimal enhancement of cytotoxicity after a 4-h exposure to high concentrations [35]. In addition, clones of HCT-8 cells have been selected which are resistant to short-term exposure to high concentrations of 5-FU, and those which are resistant to long-term exposure of low concentrations of 5-FU. Incorporation of the fluoropyrimidine into RNA was significantly decreased in the former [36, 37]. Moreover, there are clinical observations suggesting that the duration of a bolus injection of 5-FU (more or less than 5 min) may influence the clinical results (B. Gustavsson, personal

communication). Possibly prolonged exposure mainly acts by inhibition of TS by the active metabolite FdUMP, which is further enhanced by 5,10-methylenetetrahydropholate [38]. Speculatively, short exposure times might kill tumour cells predominantly by incorporation of other 5-FU metabolites into their RNA. The formation of these metabolites or their incorporation into RNA is not enhanced by folinic acid.

Since there are a number of possible mechanisms by which IFN might potentiate the cytotoxic effect of 5-FU [39], the timing and doses of IFN injections differed somewhat in the three treatment regimens. For instance, it was given every second day during the first 5 days of continuous infusion in regimen A, but daily in regimens B and C. Although the patients in this study were not randomised, our impression is that regimen B was more effective than regimens A and C.

Speculatively, the high response rate of regimen B could have been due to the fact that these patients received alternating long-term infusions (5 days) and short bolus injections (<5 min) of 5-FU. Such a 5-FU regimen was not used in the two randomised trials described above [25, 26]. The patients of group A only received 5-FU as relatively long-term infusions (5-day and 1-h infusions) and the patients of group C only received 5-day infusions. The role of doses and dose intensities of IFN for the clinical activity of the three treatment regimens is unknown. Thus, it is not known whether IFN may modulate the activity to the same extent when 5-FU is given as an infusion or as a bolus injection.

Toxicity profiles differed somewhat between the three treatment regimens. The most prominent difference was that most patients treated by regimen A complained of fatigue, which was linked to the high IFN doses. Stomatitis was observed in approximately 35% of the patients, irrespective of treatment regimen. In order to prevent or mitigate this side-effect, the patients had several daily mouth washings with allopurinol during and after the 5-day infusions of 5-FU, as described by Tsavaris *et al.* [40].

In conclusion, our results have confirmed that a combination of 5-FU and IFN can be highly effective in the treatment of advanced CRC, as far as treatment response is concerned. We do not yet know whether there is any relationship between treatment response and survival.

The treatment is relatively well tolerated in most patients and comparatively cost effective, since the 5-day infusions can be given by a continuous infuser attached to a waist-belt without hospitalising the patient. In our opinion, pharmacokinetic studies of 5-FU, formation of active 5-FU metabolites in the tumours and intratumoral levels of enzymes, such as TS, should be determined in future trials in order to further improve the treatment schedules.

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Prognostic Parameters in Localised Melanoma: Gender Versus Anatomical Location

C.P. Karakousis and D.L. Driscoll

Extremity location and female gender are both considered favourable prognostic parameters in primary melanoma, but since they cluster in the same group of patients, the question remains as to whether they are both independent variables. Multivariate analysis of 695 patients with primary, localised melanoma was used. The effects of gender and anatomical location were compared directly by sequentially controlling one factor while the other remained free. Following multivariate analysis, significant prognostic factors related to survival were the thickness of the primary lesion ($P < 0.0001$), the age of the patient at diagnosis ($P < 0.0001$), the gender of the patient ($P = 0.0008$) and the anatomical location of the primary lesion ($P = 0.005$). Thicker lesions, patients older than 50 years, males, and trunk, head and neck locations had poorer prognoses. There was a significant difference in survival according to gender within each location, extremity ($P = 0.002$) or trunk, head and neck ($P = 0.0004$); however, there was no significant difference in survival according to anatomical location within each gender, male ($P = 0.11$) or female ($P = 0.29$). The thickness of the primary lesion, the age of the patient at diagnosis, the gender and the anatomical location of the melanoma are all significant prognostic parameters in localised melanoma. Gender appears to have a more pronounced effect on survival than anatomical location.

Key words: localised melanoma, prognostic parameters
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INTRODUCTION

THE MICROSTAGING METHODS already developed have provided significant prognostic information, put surgical treatment on a rational basis and made possible the assessment of a treatment effect for a truly comparable group of controls in adjuvant studies [1, 2]. Of the two methods, the measurement of thickness has been found to provide more accurate prognosis, although both methods are still being used in pathology reports describing the primary lesion.

Other prognostic parameters reported in the literature have been the presence of ulceration in the primary lesion [3], anatomical location [3], and the gender of the patient [4]. Extremity melanomas were generally reported to have a better outlook than trunk melanomas [3]. Some reports indicated that for the so-called BANS area of skin (upper back, upper posterior arm, neck and scalp) the prognosis was poorer [5] than that for melanomas from the skin of other anatomical areas. The prognostic importance of BANS, with the exception of scalp