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Phase II Trial of 5-Fluorouracil and Recombinant Interferon Alfa-2B in Metastatic Colorectal Carcinoma

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Between February 1990 and April 1991, 59 previously untreated patients with progressive and/or symptomatic metastatic colorectal carcinoma were enrolled in a phase II study of 5-fluorouracil (5-FU) and interferon alfa-2b (IFN-α). 5-FU 750 mg/m²/day was administered as continuous infusion for 5 days, then weekly in a dose of 750 mg/m² as intravenous push injection starting on day 15. IFN-α 9 MU was given subcutaneously three times a week. Treatment was given for a maximum of 6 months. 55 patients are evaluable for response and 51 for toxicity. 17 patients (31%) achieved a partial remission, 15 (27%) had stable disease and 21 patients (38%) had progressive disease. Median duration of remission was 5 months and median survival for all patients 10 months. Toxicity was important with two treatment-related deaths and severe leukopenia, fever, diarrhoea and mucositis in about one third of the patients. In our opinion, this regimen is effective but rather toxic in metastatic colorectal carcinoma.
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INTRODUCTION

METASTATIC COLORECTAL carcinoma remains a major challenge. Wadler *et al.* [1, 2] reported high remission rates of 76 and 63%, respectively, in 17 and 32 previously untreated patients with advanced colorectal carcinoma, using a combination of interferon α-2a (IFN-α) and 5-fluorouracil (IFN-α/5-FU). Stimulated by these results, in February 1990 a group of oncologists in Hamburg working both in hospitals and private practice started a confirmatory phase II study in patients with metastatic colorectal carcinoma using the same regimen as applied by Wadler *et al.*

PATIENTS AND METHODS

Between February 1990 and April 1991, 59 patients with metastatic colorectal carcinoma entered the study. The main inclusion criteria were: histologically proven metastatic colorectal carcinoma; no possibility of surgical therapy with curative intention; bidimensionally measurable disease; no prior chemotherapy; documented progressive disease and/or symptomatic disease; Karnofsky performance status ≥50% (ECOG 0–2); adequate bone marrow function with a white blood cell (WBC)count >3000/μl and a platelet count >100 × 10^3/μl, adequate renal function with a serum creatinine level <2.0 mg/dl

and adequate hepatic function with a serum bilirubine level <2.0 mg/dl; and informed consent of the patient.

The study design was almost identical to that proposed by Wadler *et al.* [1]. 5-FU 750 mg/m²/day was administered as continuous infusion for 5 days, then weekly in a dose of 750 mg/m² as intravenous push injection starting on day 15. IFN-α (Intron A, ESSEX Pharma) 9 MU was given subcutaneously three times a week. 5-FU doses were reduced to 75% in cases of diarrhoea, mucositis, leukopenia and thrombocytopenia grade III; in grade IV toxicities it was permanently reduced to 50%. IFN doses were reduced to 5 MU if grade II neurotoxicity or fever occurred, in spite of non-steroidal antipyretic drugs. Interferon was stopped in grade III and IV neurotoxicity. Prior to therapy the following examinations were performed: medical history, physical examination, routine biochemical profile, tumour markers CEA and Ca 19-9, electrocardiogram (ECG), chest X-ray, computed tomography (CT) scan and/or ultrasound of the abdomen.

Response to therapy was routinely evaluated after 3 and 6 months of treatment and after 6 weeks whenever progressive disease (PD) was suspected. Therapy was discontinued in the case of progressive disease and in the case of stable disease (SD) after a treatment of 3 months without improvement of the patients' clinical condition. In cases of remission or SD with improvement of the patients' clinical condition therapy was continued for a total of 6 months and then stopped. When therapy had to be stopped due to PD or SD, or PD occurred after a transient remission, further treatment was not defined. WHO criteria for response and toxicity were used [3].

RESULTS

55 of the 59 patients enrolled in the study were eligible for evaluation of response. The clinical data of these patients are given in Table 1 . Treatment results were: 17 partial remissions (PR) (31%), 15 SD (27%), 21 PD (38%) and two treatment-related deaths (4%).

In 16 of 17 patients, remission was achieved after 3 months of therapy, and in 1 patient after 6 months. Median duration of remission was 5 (range 3–16) months.

Table 1. Clinical data of 55 patients evaluable for response

	No. of patients
Median age (range)	59 (25 – 76) years
Male / female	25/30
Karnofsky index	
70 – 100% (ECOG 0 – 1)	48
50 – 60% (ECOG 2)	7
Primary site of tumour	
Colon	38
Rectum	17
Prior treatment	
Surgery for primary tumour	54
Surgery for metastases or local recurrence	8
Radiotherapy	3
None	1
Time interval	
Primary tumour/ metastatic disease	
< 1 year	37
> 1 year	18
Localisation of metastases	
Liver	38
Lung	15
Lymph nodes	9
Bone	4
Peritoneum	10
No. of sites of metastases	
1	34
≥2	21
Liver involvement (n=38)	
<25%	10
25–75%	9
>75%	19
CEA (n=52)	
< 200 ng/ml	35
> 200 ng/ml	17
LDH (n=52)	
< 500 U/l	42
> 500 U/l	10
WBC (n=51)	
$< 10 \times 10^9$/l	42
$> 10 \times 10^9$/l	9

Influence on response rates

Taken together most of our patients had poor prognostic characteristics. Of the initial clinical parameters only the number of sites of metastases proved to be of influence on response rates. Of borderline significance was Karnofsky performance status. 14 of 32 patients with one site of metastases responded to therapy, but only 3 of 21 patients with two or more sites (P=0.035) responded. None of the 7 patients with ECOG 2 performance status achieved a remission, whereas 17 of 48 patients with ECOG 0 – 1 did achieve remission (P=0.08). All other variables tested, such as age, sex, primary site of tumour, time interval, primary tumour/metastatic disease, extent of liver involvement, CEA, lactic dehydrogenase (LDH) and WBC had no influence on remission rate.

Of course, these findings should be considered with caution because of the small number of patients and the unequal distribution of variables inside each prognostic factor.

Dose intensity and response rate

The planned dose intensity for 3 months of treatment was 27 × 10^6 U per week IFN-α and 865 mg/m² per week 5-FU. Patients achieving a PR after this period of treatment had received a median dose intensity of 21.5 × 10^6 U per week IFN-α and 647 mg/m² per week 5-FU, those with SD had had 21.5 × 10^6 U per week and 684 mg/m² per week and those with PD had received 24 × 10^6 U per week and 805 mg/m² per week. The differences were not statistically different.

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Table 2. Main toxicities in 51 patients

	WHO grade				
	0	1	2	3	4
Leukopenia	13	4	19	11	4
Fever	14	11	25	1	0
Diarrhoea	21	5	9	14	2
Fatigue	22	25	3	1	0
Hair loss	27	17	7	0	0
Mucositis	24	12	5	9	1
Nausea/vomiting	28	15	5	2	1
Anaemia	31	10	8	2	0
Thrombocytopenia	35	11	4	1	0
Infection	44	3	1	1	2
Rash	44	5	2	0	0
Neurotoxicity	44	5	1	1	0

Survival

33 patients have died and 22 patients are living (November 1991). Median survival for all 55 patients is 10 months, for those with PD 4 months, and probability of median survival for patients with SD or PR is 14 months and not yet reached after 21 months, respectively.

Toxicity

Main toxicities are known in 51 patients and are given in Table 2. In 4 patients evaluable for response, toxicity was documented irregularly and they are therefore not included in the analysis. Roughly, this regimen was very toxic in about one-third of the patients, with leukopenia, fever, diarrhoea and mucositis being clinically most important. This regimen led to two treatment-related deaths. Both patients developed leukopenia grade 4, watery diarrhoea, dehydration and sepsis after 3 and 4 weeks of treatment, respectively. Toxicity developed in most patients some days after 5-FU injection. There was no clear correlation between severity of toxicity and duration of treatment.

DISCUSSION

After the publication of the results of Wadler *et al.* [1, 2] reporting on a remission rate of 76 and 63% in patients with previously untreated metastatic colorectal carcinoma, several phase II studies were published using the same 5-FU/IFN-α regimen or a slight modification thereof [4–11]. Although the effectiveness of this regimen was confirmed, none of the reports confirmed the high remission rate reported by Wadler *et al.* [1, 2]. In the confirmatory studies, remission rates generally ranged between 25 and 40%. In this respect, the present large phase II study confirms our previous findings [11] and the remission rate of 31% is well in accordance with other reports. Nevertheless, it should be emphasised that our patients represented a poor risk group so that the remission rate of 31% is remarkable. Duration of remission and survival are no main endpoints of phase II studies, but the reported data [2, 4–10], as well as our findings with a median duration of remission of 5 months and a median survival of 10 months, are in the same range as with 5-FU/FA regimens [12].

Response to therapy in our patients was influenced by the number of sites of metastases and, though it failed statistical significance, by Karnofsky performance status. This is in contrast with the findings of Kemeny *et al.* [13], where none of these factors was related to response. It may be hypothesised that treatment with 5-FU/IFN has changed the natural history of disease. Possibly, additional parameters, such as extent of liver involvement [13, 14], would have been of importance in a study comprising more patients.

Hryniuk *et al.* [15] has shown that in colorectal cancer, too, a strong correlation exists between dose intensity of 5-FU and response rate. In our study, dose intensity of 5-FU was high and ranged between 647 and 805 mg/m^2 per week during the first 3 months of treatment.

This regimen was very toxic in about one third of the patients. Leukopenia, diarrhoea, mucositis and fever were serious side-effects. The rate of severe gastrointestinal toxicity was in the same range as with 5-FU/FA regimens [12, 16], but it must be emphasised that our dose reduction criteria for 5-FU resulted in high doses of 5-FU. In other studies [5, 16], doses of 5-FU were permanently reduced when diarrhoea grade I or II occurred. Other investigators using 5-FU/IFN regimens have seen these complications as well as neurotoxicity in a comparable rate [4–7, 10]. It is unclear why neurotoxicity was not severe in our patients. By contrast, in a group of patients roughly comparable with ours, Kemeny *et al.* [5] had seen severe neurotoxicity in 34%. Most important, 2 of our patients died due to toxicity. Wadler and Wiernick [2] also lost 2 patients because of diarrhoea and sepsis. One toxic death was reported by Pazdur *et al.* [4] and two deaths by Diaz Rubio *et al.* [10]. The toxic death rate of 2–6% in the 5-FU/IFN regimens is quite comparable with that seen in 5-FU/FA regimens. Poon *et al.* [12] reported one treatment-related death in 69 patients on the 5-FU/high-dose FA regimen and in the trial of Petrelli *et al.* [16], the death rate was 5% in the 5-FU/FA regimens.

The severe toxicity in our study supports Wadler's statement that this therapy should not be given outside of clinical trials with the possibility of optimal supportive care. When modifiying the doses of both drugs according to the toxicities encountered toxicity may be acceptable, as has been recently shown in a multi-institutional setting [8].

In summary, the combination of 5-FU and IFN-α is undoubtedly an effective but toxic regimen in metastatic colorectal cancer. Because of toxicity, dosage and schedule of both drugs should be modified in further trials. The precise impact of interferon-α in this regimen and the comparison with the frequently used 5-FU/FA combination must be studied in large phase III trials.

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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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