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FROM THE DEPARTMENT OF MEDICAL ONCOLOGY AND RADIOTHERAPY, THE NORWEGIAN RADIUM HOSPITAL, MONTEBELLO, N-0310 OSLO 3, NORWAY.

SEQUENTIAL 5-FLUOROURACIL AND METHOTREXATE

Negative experience in metastatic colorectal cancer

E. HOFF WANDERÅS, S. D. FOSSÅ, K. M. TVEIT and A. FLOKKMANN

Abstract

Forty-two patients with measurable advanced colorectal cancer were treated with sequential methotrexate (MTX) and 5-fluorouracil (5-FU), followed by folinic acid rescue. Twenty-one patients had received prior chemotherapy, mainly 5-FU (group 1) and remaining 21 patients had not been previously treated by cytotoxic agents (group 2). Two different treatment schedules were used. Regimen I (27 patients): MTX 250 mg/m^2 was infused over 1 hour. Two hours from start 5-FU 600 mg/m^2 was given as intravenous bolus. Folinic acid rescue started 24 hours after MTX infusion. Regimen II (15 patients): MTX 250 mg/m^2 was given as 1-hour infusion. Three hours after the start of MTX a 46-hour 5-FU infusion (2000 mg/m^2) was started. Folinic acid rescue as in regimen I. The chemotherapy courses were repeated every second week. After 3 cycles only one patient had partial response, 33 had no change and 8 progressive disease. The median time until progression was 2 1/2 months in group 1 and 4 months in group 2. The median survival was 7 months in group 1 and 10 1/2 months in group 2. Almost identical results were obtained by the two treatment schedules. The toxicity of both regimens was low.

Key words: Colorectal neoplasms; advanced carcinoma, methotrexate, 5-FU.

According to the literature, 5-fluorouracil (5-FU) has a response rate of 15 to 20 per cent in metastatic colorectal carcinoma (3, 16).

Experimental and clinical studies have indicated an improved response rate if 5-FU is preceded by methotrexate (MTX) (7, 12). The interaction between these two drugs is complex, but there is evidence for a synergism between MTX and 5-FU (5, 6).

Several clinical studies have been published concerning combination therapy with MTX and 5-FU in patients with metastatic colorectal cancer (2, 9, 11–13, 17–20). The reported response rates range widely between 5 and 50 per cent.

Sequential combination treatment with MTX and 5-FU in metastatic colorectal cancer was introduced at the Norwegian Radium Hospital in 1982. As a result of the reports on the optimal interval between MTX and 5-FU administration, the initial treatment regimen was altered late in 1984 when the interval between the MTX and 5-FU application was prolonged from 2 to 3 h. Simultaneously, the 5-FU dose was increased within each cycle. The present report deals with the response rate and the toxicity observed in patients with and without prior chemotherapy.

Material and Methods

The study comprises 42 consecutive patients with bidimensionally measurable metastatic colorectal cancer. Twenty-one patients (group 1) had received prior cytostatic treatment (5-FU, $n=19$, d-fluorodeoxyuridin, $n=1$, epidoxorubicin, $n=1$). All chemotherapy was discontinued at least 4 weeks before start of MTX/5-FU. Another 21 patients (group 2) had not received any previous cytostatic treatment. Table 1 gives further details of the two groups which were comparable for most parameters. However, the median interval from initial diagnosis to detection of metastases was twice as long in group 1 as in group 2. Nine of the patients in group 2 had metastases at the time of diagnosis compared to 5 in group 1. In group 1 the majority of patients received regimen I whereas most patients from group 2 were treated by regimen II.

MTX/5-FU chemotherapy was given sequentially by two consecutively used regimens.

In regimen I MTX 250 mg/m^2 was administered for 1 h. Two hours from start 5-FU 600 mg/m^2 was given as an injection. Rescue treatment with folinic acid (leucovorin)

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Table 1
Patients' characteristics

	Total	Group 1 Previous cytostatic treatment	Group 2 No previous cytostatic treatment
No.	42	21	21
Age, median (range)	62 (28–77)	59 (28–77)	62 (41–77)
Performance status			
0–1	34	15	19
2–3	8	6	2
Site of primary tumour			
Rectum	17	6	11
Colon	25	15	10
Prior radical surgery	21	10	11
Hist. diff. grade			
Low	11	4	7
Median	31	17	14
High	0	0	0
Metastases at primary diagnosis	14	5	9
Median interval in months from primary diagnosis to discovery of metastases (range)	9 (0–156)	12 (0–156)	6 (0–66)
Indicator metastases			
Lung	16	10	6
Liver	16	7	9
External lymph nodes	5	1	4
Liver + lung	1	0	1
Chemotherapy			
Regimen I	27	18	9
Regimen II	15	3	12

10 mg/m^2 was initiated 24 h from start of the MTX infusion and repeated every 6 h until the MTX serum level was below 80 mg/l. This treatment was given to 18 patients in group 1 and 9 in group 2.

In 1984 the treatment was altered. In regimen II MTX 250 mg/m^2 was given as a 1-h infusion on day 1, followed by 5-FU 2000 mg/m^2 as a 46-h infusion starting 3 h after the initiation of the MTX infusion. Leucovorin rescue was identical to that used for regimen I. Three patients of group 1 and 12 of group 2 received MTX/5-FU according to regimen II.

The MTX/5-FU treatment was repeated at 2-week intervals for a maximum of 6 courses, thereafter at 3-week intervals. Treatment was usually continued until progression or—in case of no change—until the patient had received 10 cycles. One patient received 15 cycles. After discontinuation of MTX/5-FU the patients with no change continued with weekly 5-FU injections.

Response was evaluated after three cycles according to the WHO criteria (15). Measurements were based on clinical examination, ultrasonography to show hepatic metastases and chest radiography to show lung metastases. In addition, serum carcinoembryonic antigen (CEA) was analysed before each chemotherapy course (8).

Results

None of the 42 patients had complete response (CR) (Table 2). One patient from group 1 had partial response (PR) of lung metastases on regimen I which lasted 29 weeks. Thirty-three patients had no change (NC) after 3 cycles. At treatment discontinuation, 7 patients had NC and 35 had progression (PD).

The median time to progression in patients with no change after 3 cycles was $2^1/_2$ months in group 1 and 4 months in group 2. In patients with NC on regimen I the median time to progression was 3 months, whereas the comparable interval was 4.3 months in patients treated by regimen II. At treatment discontinuation, 7 patients had NC and 35 had progression.

The median survival from start of MTX/5-FU treatment was 7 months in group 1 and $10^1/_2$ months in group 2, with no difference between patients on regimen I and those on regimen II.

In only 10 of 35 patients the clinical response was mirrored by comparable changes of the serum CEA levels after 3 MTX/5-FU cycles (Table 3). At treatment discontinuation the correlation between clinical response and serum CEA changes was also unsatisfactory. Only 17 of the 30 clinically progressing patients had increasing serum

Table 2
Treatment results

	Group 1 (n=21)	Group 2 (n=21)
Response after 3 courses		
CR	0	0
PR	1	0
NC	13	20
PD	7	1
Median duration (months) of NC (range)	2 1/2 (1–7)	4 (2–>6)
Median survival (months) from start MTX/5-FU (range)	7 (2–15)	10 1/2 (2–22 1/2)

Table 3
CEA changes in various response groups of treated patients after 3 courses and at discontinuation

Response	Total	Reduction		Unchanged	Increased
		>50%	<50%		
CEA after 3 courses					
PR	1	0	0	1	0
NC	28*	5	12	5	6
PD	6*	0	1	0	5
CEA at discontinuation					
NC	3**	0	1	0	2
PD	30**	4	4	5	17

* Values not measured in 7 patients.
** Values not measured in 9 patients.

CEA and 8 of these patients had even decreased CEA levels.

The treatment with MTX/5-FU was well tolerated, especially in the group which received regimen I. Moderate nausea and vomiting occurred in only 6 of the 42 patients. These symptoms were most dominant the first 1 to 3 days after treatment. Six patients complained of diarrhoea, 6 showed mucositis and 7 had a slight conjunctival injection. Eighteen patients complained of fatigue. Only 2 patients (group 1) developed leucopenia (1.5–3.0 $\times$ 10^9/l), whereas thrombocytopenia (<100 $\times$ 10^9/l) was not seen at all.

Discussion

The results in our study which showed only one PR in 42 patients, were inferior to those reported in the literature (Table 4). Admittedly, some of the 33 patients with NC after 3 cycles had a minor reduction of the indicator lesions but this was not sufficient to qualify for classification as PR. Interestingly, the median survival rates in our study were comparable to those found in other studies in spite of our low response rate (1, 12, 18,19).

The low objective response rate in the present series can partly be explained by the well-known difficulties involved in measuring indicator lesions in patients with colorectal cancer (10). Liver metastases—the most frequent distant secondaries—are difficult to assess. Neither repeated routine clinical evaluation nor ultrasonography yield reproducible measurements.

The drug scheduling of MTX and 5-FU may also explain the low response rate. According to in vitro and in vivo laboratory studies the optimal interval between MTX and 5-FU administration has not been exactly defined, but is probably in the range of 6 to 24 h (4, 5). The interval between application of the two drugs in the first treatment regimen was only 2 h, which was possibly too short to yield an optimal cytostatic effect. This interval, however, should theoretically be adequate in the second regimen. The 5-FU dose was also increased considerably and given over 46 h. In spite of this change of the treatment no

Table 4

Response, median duration of response and survival in different published studies

Author year	Ref.	CR+PR (%)	Median duration of response	Median survival
Herrmann (1984)	(12)	38 (16/42)	7.5	13.5
Cannobio (1986)	(9)	5 (1/20)	3	7.5
Panasci (1985)	(17)	28 (7/25)	6	>15
Rabinovich (1984)	(18)	15 (3/20)	3.67	6
Kemeny (1984)	(13)	32 (14/43)	9	-
Weinermann (1982)	(20)	42 (10/24)	4	-
Ajani (1985)	(2)	30 (1/3)	3.5	-
Tismann (1980)	(19)	30 (--)	6	5
Glimelius (1986)	(11)	50 (25/50)	5	19 (CR) 11 (PR)
Present series		2.5 (1/42)	7.5	12

improvement in treatment results was seen. The reason may be the short elimination time of 5-FU from blood and tumour tissue. A therapeutically sufficient concentration of the active metabolite of 5-FU was possibly never obtained by the continuous administration. Bolus injections or rapid infusions of 5-FU, given at least 3 to 4 h after MTX, are probably more effective. Unfortunately, no pharmacokinetic measurements were made in our study.

Admittedly, the total 5-FU dose per cycle was low, especially regarding the first regimen. In view of the low hematologic and subjective toxicity the 5-FU dose could have been increased, which might have given a higher response rate.

The fact that a patient with progressing disease on 5-FU single drug treatment responded to MTX/5-FU may be explained by the above mentioned synergistic effect of MTX and 5-FU. On the other hand, the previous 5-FU treatment may have been insufficient since he had received oral 5-FU which has an unpredictable absorption rate from the gastrointestinal tract.

The discrepancies between CEA changes and clinical response probably indicate a heterogeneity of the cancer cell population in patients with colorectal cancer. CEA-producing cancer cells may respond differently to cytostatic treatment than tumour cells without CEA production. The present study confirms previous findings stating that CEA measurements are of limited value as monitors of response to cytostatic treatment (1).

In conclusion, the sequential administration of MTX/5-FU as applied in the present study showed minimal activity in metastatic colorectal cancer and does not seem to be superior to conventional 5-FU treatment. The lacking efficacy may be due to the low 5-FU doses applied. Though not very toxic, the combination treatment is more resource demanding than 5-FU alone and cannot be recommended for the treatment of metastatic colorectal cancer. Other ways of sequencing and dosing may, however, turn out to be more effective.

Request for reprints: Dr Sophie D. Fosså, Det Norske Radiumhospital, Montebello, N-0310 Oslo, Norway.

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