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Sequential Methotrexate–5-FU–Leucovorin (MFL) in Advanced Colorectal Cancer

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Abstract—*Methotrexate* (MTX) (250 mg/m^2) *was given as an i.v. infusion over 2 hr. At hour three and* 23, *5–FU* (500 mg/m^2, *maximally* 1000 mg) *was given as a bolus i.v. injection. The Leucovorin rescue was initiated hour* 24. *The chemotherapy course was repeated every* 14 days *for eight courses, then every third to fourth week. At least four courses of the regime were given to* 50 *patients with measurable advanced colorectal carcinoma. Toxicity was usually very mild but in seven patients an increase of serum creatinine was registered. Two of these patients had a severe period of uremia. With a more careful observation of kidney function, these episodes should have been foreseen. An objective response rate of* 50% *with six complete remissions (CR) and* 19 *partial remissions (PR) was found. Eighty-eight per cent* (21/24) *of the patients with tumour-related symptoms experienced symptomatic relief. The median response duration amounts to* 5 months. *It is concluded that the MFL regime is effective in inducing anti-tumour response in patients with advanced colorectal cancer.*

INTRODUCTION

In several experimental tumour systems, a synergistic effect on tumour cell kill has been demonstrated by sequentially delivered MTX and 5-FU [1, 2]. Earlier studies on murine systems showed that a time interval of 1 hr was sufficient for synergistic effect, whereas a later study using human tumour cells has indicated a longer time interval, of 18–24 hr, for optimum cell kill [3]. Using murine and human tumour cells *in vitro* a cytotoxic activity by 5–FU was potentiated several-fold when an excess of folinic acid (Leucovorin) was added to the culture medium [4, 5]. Although considerable knowledge has been acquired concerning the biochemical basis for these interactions, they are clearly complex and vary depending upon cell origin and growth rates [6–8].

In several, usually small and preliminary clinical series, sequentially derived MTX and 5–FU followed by Leucovorin rescue has given high response rates [9–11]. In colorectal cancers, the objective response rates have varied considerably or from 0 to 80%. The higher response rates were usually found when a time interval of 4–7 hr or longer was used compared to when only a 1-hr interval was used [12, 13]. The dosage schedules have, however, not been uniform.

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The optimum clinical dosage schedule of sequential MTX/5–FU and the integration of Leucovorin has not been established. Based upon the present knowledge together with some assumptions, a somewhat different approach to deliver the drugs was designed. To define the toxicity and to test the relevance of this approach, a preliminary clinical study was performed.

MATERIALS AND METHODS

Patients

From November 1982 until August 1984, 71 non-selected patients below 76 years of age (median 65, range 32–75 yr) with an advanced colorectal carcinoma were seen at the Department of Oncology in Uppsala, Sweden. Thirty-eight of the cases had their primary tumour in the rectum–rectosigmoideum, and the remaining 33 in the colon. Thirty-four of the patients were male. The time from diagnosis of their primary tumour ranged from 0.5 to 84 months (median 16).

The treatment was initiated in all 56 patients who had measurable disease, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, serum creatinine levels below 120 mmol/l, and no clinical signs of pleural effusions or ascites that could not be adequately removed. Seventeen of the patients had an ECOG performance status of 0, 28 patients had 1, and 11 patients 2. In asymptomatic patients with lung metastasis only, treat-

ment was not initiated until the disease was progressive (>25% increase or new lesions, see below). The remaining 15 patients had either non-measurable disease (six cases), elevated *S*-creatinine levels (one case), a performance status of 3 or more (seven cases) or massive effusions (one case). Fifty of the patients received at least four courses of treatment and could be evaluated for therapeutic response. Six patients did not complete four courses, and were considered non-evaluable for therapeutic response. The reasons were in two cases development of ileus symptoms that required laparotomy between the second and third treatment course (both patients had repeated severe subileus attacks prior to the initiation of treatment), one patient had an excellent symptomatic relief after two courses and chose not to continue treatment, and three patients died shortly prior to the second and third (two patients) course, respectively, from the disease; at least one of the patients had experienced symptomatic relief from the treatments.

Seven of the 50 evaluable patients had received prior chemotherapy, either 5–FU alone or a combination containing 5–FU, CCNU and vincristine; all those patients had shown progressive disease during their previous chemotherapy. Nineteen patients had received prior radiotherapy to the pelvis. The time interval between the end of the radiation therapy and the initiation of chemotherapy treatment was at least 3 months.

Treatment

Table 1 illustrates the chemotherapy protocol. All patients received $NaHCO_3$ 2 g × 4 for 2 days to alkalize the urine. No special hydration programme was used. Treatment was repeated every 14 days for eight courses, every third week for two more courses and then every fourth week. Doses were reduced according to a dose reduction scheme (Table 1). A dose reduction to 0% resulted in postponement of the treatment for 1 week. If the *S*-creatinine levels increased by more than 30% or above 125 mmol/l, treatment was interrupted, and the reason was looked for. If the reason was a postrenal stasis, and the *S*-creatinine levels could be normalized after appropriate procedures, the chemotherapy was reinstituted.

The evaluation criteria for objective responses followed the UICC recommendations originally described for mammary carcinoma [14]. The first evaluation of response was made after the fourth treatment course, except in cases with local pelvic growth measurable only on CT–scans, where the first evaluation was made after eight courses. Liver involvement and intraabdominal involvement was measured on CT-scans or, in a few cases, using ultrasonography. If the patients showed disease progression after four courses, the treatment was interrupted. If no objective response was present after eight courses, treatment was also discontinued. For the responders, the treatment continued either until progression was noticed or as long as the treatment was considered "excellent palliation". The treatment has been interrupted at least temporarily in some patients in continuous response after 9–20 courses in spite of no adverse effects from this treatment.

RESULTS

Treatment response

Six (12%) of the patients who completed four treatment courses had a CR, 19 (38%) a PR and 24 patients had no response. Of the latter patients no change (NC) was noticed in 14 patients, whereas the remaining patients had progressive disease (PD) (Table 2). All three patients with pulmonary metastasis and a CR had multiple lesions ranging in size between 1 and 2 cm on chest X-rays; those lesions had increase in size, or number, during the 2–3 months proceeding the chemotherapy. One patient with a diffuse intraperitoneal carcinomatosis discovered at surgery for the primary tumour had a laparatomy-verified CR after 11 courses, one patient with a primarily inextirpable rectal tumour with remaining biopsy-verified viable tumour 3 months after the end of pelvic irradiation (62 grey in 8 weeks) also had a laparotomy-verified CR after 12 courses, and finally, one patient with a 2 × 2½ cm large metastasis in the abdominal wall measurable with ultra-sonography also had a CR.

No objective response was obtained in the group of patients who had received prior chemotherapy (Table 2). Four of those patients had, however, a disease stabilization lasting at least until the start of the ninth course (4½ months); all those patients had shown progressive disease during their previous chemotherapy. The response rate was not different due to site of primary tumour, age and sex, initial performance status or disease-free interval (data not illustrated), and it was not apparently different due to site of measurable disease (Table 3). The response rate of liver metastasis was 44% (8/18) when all patients were included and 57% (8/14) when only those patients who had not obtained previous chemotherapy were included. The evaluation of response for patients with local pelvic growth was difficult, particularly when the tumour was not palpable, i.e. measurable only on CT. None of the latter patients showed any change in the size of their pelvic mass, although a tumour response could have been suspected since several of those patients had an excellent symptomatic benefit for up to 9 months (see below). Further, when the pelvic tumour in addition was palpable, some

Table 1. *MFL-treatment schedule*

Time of administration	Drug	Dose
Hour 0 to 2	MTX	250 mg/m^2 i.v. infusion
At hour 3	5–FU	500 mg/m^2 (max 1000 mg) i.v. push
At hour 23	5–FU	500 mg/m^2 (max 1000 mg) i.v. push
At hour 24	Leucovorin	15 mg i.m.
At hour 30 and every 6 hours for 7 doses	Leucovorin	15 mg p.o.

Dose reduction scheme

B–LPK	B–TPK	MTX	5–FU
(× 10^9/l)		(% of planned dose)	
2.1–2.9	100–125	100	75
1·5–2.0	75–99	100	50
<1.5	<75	0	0

Table 2. *Results of the MFL-regimen in patients with colorectal cancer*

	CR	PR	NC	PD	Total	Objective response rate (%)
	(Number of patients)					
Previously untreated	6	19	10	8	43	58
Previous chemotherapy	0	0	4	3	7	0
Total	6	19	14	11	50	50

Table 3. *Objective responses in relation to measurable metastatic site(s)*

	CR	PR	NC	PD	Total	Objective response rate (%)
	(Number of patients)					
Lung	3	5	2	3	13	62
Liver	–	8	4	6	18	44
Intraabdominal mass	1	4	3	–	8	63
Local pelvic growth	1	5	7	1	14	43
Others	1	2	4	1	8	38

patients had a marked reduction in tumour size, but the mass at CT was unchanged or showed only minor decrease; those patients were classified as having PR or, in one case (see above) CR.

The median objective response duration was 5 months with a range from 2 to 10 months (CR median 8, range 5–10; PR median 4, range 2–10). One of the patients in CR ended her remission in brain metastases after 8 months, and a second patient with a partial remission for 3 months also developed brain metastases. Median survival was 19 months (range 8–27+) for the patients with a CR, 11+ months (range 5–22+) for those with a PR, 10 months (range 5–28+) for those with NC

and 5 months (2–19) for those with PD.

Twenty-four of the 50 patients had subjective symptoms (e.g. pain in 14 patients, secretion in eight patients) that were caused by their tumour manifestation. All but three patients showed either a complete disappearance of the symptoms (10 patients) or a significant reduction. This symptomatic relief was in several cases very rapid and noticeable already after the first treatment course. The median duration time of subjective remissions was 4 months (range 1–9 months). Three of the patients who had obtained previous chemotherapy had in addition to an objective disease progression also progressive symptoms while on their prior therapy. All those patients experienced considerable symptomatic benefit from the MFL regime lasting between 4 and 8 months.

Treatment tolerance

Six patients had four treatments only (interrupted because of disease progression), 18 patients between five and eight treatments (interrupted because of no response, rising creatinine level or death), 17 patients between 9 and 12 courses, eight patients between 13 and 24 courses, and one patient so far 37 courses. There was a total of 494 treatment courses in the 50 patients. Toxicity which was evaluated in all 56 patients where therapy was initiated was usually very low but with some severe toxic effects. Twenty-eight patients developed conjunctivitis, 25 patients gastrointestinal toxicity, usually mild to moderate nausea or slight diarrhoea of a short duration, 10 patients noticeable alopecia and five patients experienced increased fatigue after prolonged treatment (Table 4). It should be noted, however, that several patients had to travel up to 500 km every 14 days, because it was considered preferable to deliver all treatments at the same ward. These adverse effects were usually not noticed until after 6–8 courses. Bone marrow depression with a white blood cell (B–LPK) count below 1.5×10^9 that required prolongation of the treatment interval for 1 week, was noticed only in six patients, and then not before the sixth treatment course. No patient had any episode of fever or infection that could be related to neutropenia. Two patients had slight thrombocytopenia. Seven patients had an increase of the *S*-creatinine level; in five it was minor (125–155 mmol/l), but in two cases it was severe, 1710 and 1380 mmol/l, respectively. In all patients the *S*-creatinine was normalized completely after discontinuation of the chemotherapy and in four of the patients (in both with a severe episode of uremia) unilateral or bilateral nephro-pyelostomia due to postrenal stasis. In retrospect, the two severe episodes of uremia should have been avoided, since these patients had an increase in their *S*-creatinine levels (130–145 mmol/l, result of stasis?) prior to their last treatment course. The significance of these moderate increases of the serum creatinine levels was not properly recognized.

One patient died suddenly 4 days after the seventh course of treatment while in partial remission. This patient had had no prior adverse effects from the treatment. The autopsy showed liver metastases and locally recurrent growth in the pelvis, both of which were known, advanced generalized cardio-arteriosclerosis and possibly slight pneumonia in the right lung, but no conclusive reason for his sudden death.

Table 4. Acute and subacute toxicity after cytostatic treatment

	Patients with toxicity grade*									
	0		1		2		3		4	
	N	%	N	%	N	%	N	%	N	%
Leukopenia	39	70	+		11	20	6	11	0	–
Thrombocytopenia	54	93	2	4	0	–	0	–	0	–
GI toxicity:										
stomatitis	47	84	6	11	2	4	1	2	0	–
nausea/vomiting	35	63	17	30	4	7	0	–	0	–
diarrhoea	44	79	9	16	3	5	0	–	0	–
Kidney dysfunction‡	49	88	5	9	0	–	0	–	2	4
Hair loss	46	82	5	9	5	9	0	–	0	–
Conjunctivitis	28	50	23	41	5	9	0	–	0	–

* WHO: Recommendations for grading of acute and subacute toxic effects.

\+ Not registered as toxicity.

‡Grade 1, 125–275; grade 2, 275–550; grade 3, 550–1110 and grade 4, > 1110 mmol/l, respectively. The upper normal value of the population under study was 108 mmol/l.

DISCUSSION

The objective response figure (50%) with several CR in this series of patients appears superior to previous series using sequential MTX/5–FU/Leucovorin (for recent reviews, see [12, 13]). When those patients in whom treatment was initiated but no evaluation could be made, (see Materials and Methods) were included, the response figure is 45% (25/26). The frequency of subjective responses (21/24, 88%) is encouraging. This latter response figure is, however, 'subjective' and therefore open to criticism, but nevertheless, of great importance. Although both the objective and the subjective responses appear high, it should be remembered that this is a preliminary series that needs confirmation in controlled clinical trials before acceptance.

The toxicity of the regime was very mild but the regime is potentially toxic mainly due to the MTX-dose. The two episodes of severe uremia occurred early in the series and could well have been avoided with a more careful control system. Since then, our routines have changed, and no further severe toxic effects have been observed. The reason for the death of one patient is not known, therefore it has been included as an unexplained toxic effect by the regime.

The present treatment schedule differs from previously used ones in two major ways. First, 5–FU is given twice, 3 and 23 hr after the initiation of the MTX infusion, and second, the Leucovorin rescue is initiated shortly after the last 5–FU dose. The first modification was included since the optimum dose scheduling interval was not known, either from experimental studies, or from clinical series. Experimental studies have indicated that different tumour cells from different species required a different time interval for maximum synergistic effect. Human tumours are known to be very heterogeneous in their response to chemotherapy (for review, see [15]). It was thus thought to be rational to deliver two 5–FU doses instead of one. A prolonged infusion of 5–FU was not chosen, since the treatment should be possible to deliver on an out-patient basis. Secondly, a second 5–FU dose was delivered close to, but not too close to (the idea was that the interaction between MTX and the second 5–FU dose was allowed for 1 hr before it was interrupted by the rescue) the Leucovorin, since a beneficial cell kill interaction can be anticipated both from theoretical grounds as well as from experimental and clinical studies [4, 5, 16, 17]. From more recent experimental and pharmacokinetic studies, it is, however, likely that the time interval between 5–FU and Leucovorin is too long and the dose of Leucovorin far too low for a beneficial cell kill effect *in vivo* [18, 19]. Although it is not at all known whether these modifications are clinically relevant, the clinical data indicate that this MFL regime and the ideas behind it justify further exploration. To this end a multicentre randomized study has been started in which the MFL regime is compared with high-dose 5–FU as single drug in patients with subjective symptoms from advanced colorectal cancer. In another study in patients without subjective symptoms, the MFL regime is compared with no initial chemotherapy.

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