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Quality of Life During Cytostatic Therapy for Advanced Symptomatic Colorectal Carcinoma: a Randomized Comparison of Two Regimens

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Abstract—*Physician- and patient-rated 'quality of life' was studied in patients receiving chemotherapy for advanced symptomatic colorectal cancer. The patients participated in a Nordic multicentre randomized study comparing single-drug 5-fluorouracil (5-FU) with a combination of sequential methotrexate–5-FU with leucovorin rescue (MFL). Forty-four patients (all patients included at one of the hospitals) entered this associated 'quality of life' study, 22 in each group. In the MFL group, five patients had a partial remission (PR) and seven prolonged stationary disease (SD), whereas in the 5-FU group, only one patient had a PR and two SD. Median survival was longer in the MFL group (9 months) than in the 5-FU group (4 months). According to the physicians' judgement, 12 (55%) of the patients randomized to MFL experienced improved 'quality of life' compared to five (23%) in the 5-FU group. Patients' ratings gave the same figure (55%) in the MFL group, whereas only two (9%) patients in the 5-FU group considered themselves improved. The correlations between physicians' and patients' ratings were good. Adverse effects of treatment were minor and influenced ratings negatively only in one patient (5-FU group). Items that reflected changes in everyday activities discriminated better than other items in the 'quality of life' assessment. Since 'quality of life' measures were better in the MFL group in this associated study, and since objective and subjective responses, changes in Karnofsky performance status (KPS) and in survival also were better in the MFL group, not only in this study but also in the Nordic trial (249 patients randomized), we conclude that MFL is superior to 5-FU as a palliative treatment.*

INTRODUCTION

PATIENTS with primarily advanced or recurrent colorectal cancer are, with few exceptions, left with palliative treatment only. Systemic cytostatic treatment is widely used for palliation. 5-Fluorouracil (5-FU) causes an objective tumour response in 5–20% of the patients with lower figures in multicentre studies than in single institution ones [1–4]. No other cytostatic drug or drug combination has yet been proved to be superior to 5-FU, although certain combinations have yielded higher response rates in uncontrolled studies [3, 5–7]. However, since survival is not prolonged [2, 7], the extent to which this therapy is of benefit for these patients is not known. An objective tumour response does not necessarily indicate that the patient experiences palliation [8, 9]. In view of the low objective response rates, the short duration of responses and the adverse effects these drugs may cause, it can be questioned whether the therapy gives valuable palliation in more than an occasional patient.

A combination of sequential methotrexate (Mtx)–5FU with leucovorin rescue (MFL) yielded a high objective response rate in a single department study [10]. In symptomatic patients, considerable symptom relief was often achieved. This combination has now been compared with 5-FU in symptomatic patients in a large prospective randomized multicentre study. The entry of patients ended in March 1987 after inclusion of 249 patients from 18 hospitals in three Nordic countries.

An associated study of patient-rated 'quality of life' was performed on the patients included in the multicentre study at the University Hospital in Uppsala, Sweden. The purpose was threefold: (1) to determine the proportion of patients in each of the treatments who experience palliation, i.e. symptomatic relief without relevant adverse effects,

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(2) to evaluate whether the MFL regimen is superior to 5-FU as a palliative treatment and (3) to compare physicians' and patients' judgement of subjective responses and adverse treatment effects. The present report describes the results from this associated study.

MATERIALS AND METHODS

Design of the Nordic trial

Eighteen hospitals in Sweden, Norway and Finland participated in a multicentre study, where patients with symptomatic, non-curable colorectal cancer were randomized to receive either 5-FU alone or MFL (see below) as their primary cytostatic drug therapy. The disease should be measurable and the patients be 75 years old or younger, have a Karnofsky performance status (KPS) 60 or higher, normal kidney function, no icterus, ascites or pleural effusion and no previous cytostatic therapy. All patients were informed according to the guidelines approved by the ethics committee. The study was initiated in January 1985. Patient entry was closed by 31 March 1987 with 249 patients included.

Treatment

Treatment should be initiated within 2 weeks after randomization (R). Patients received either two doses of 5-FU, 600 mg/m^2 i.v. bolus 24 h apart, or the MFL regimen [10] consisting of Mtx 250 mg/m^2 as an infusion during hours 0–2 followed by 5-FU 500 mg/m^2 i.v. bolus at hours 3 and 23. The leucovorin rescue was initiated at hour 24 with 15 mg i.m. followed by seven oral doses of leucovorin, 15 mg every 6 h. All patients received sodium bicarbonate 2 g × 4 for 2 days. Treatments were repeated every 14 days for eight courses and every 3–4 weeks after that. The first evaluation of response was made after four courses (C4, before the 5th course); if progressive disease was present at that time, treatment was interrupted. Treatment should not be terminated before course 4 unless severe adverse effects occured. Subsequent response evaluations were made after every 4th course. Therapy was continued as long as it was considered to be valuable palliation. In cases of treatment interruption, all therapy was individual.

Evaluation of response: physician's judgement

The evaluation of objective responses follows the UICC recommendations [11]. A complete response (CR) or a partial response (PR) should be present at two consecutive evaluations. In order to qualify as stationary disease (SD), this state should be present at the evaluation (C8) before the 9th course, corresponding to a duration exceeding 4 months. Patients who had stationary disease at C4 but who progressed before C8 are, in the present paper, designated SD/PD. In all other instances, progressive disease (PD) was present. All response durations were computed from the date of randomization to the date of progression.

The evaluation of adverse effects follows the WHO guidelines [12].

Every physician should, in addition, make a judgement of tumour related symptoms and adverse effects at each evaluation.The following categories were employed. Symptoms: free from, diminished, unchanged, increased; adverse effects: none–miniminal, slight–moderate, severe.

Quality of life assessment: patient's judgement

Patients at the Departments of Surgery and Oncology, Akademiska sjukhuset, Uppsala, Sweden, included in the Nordic study, were entered in this study after giving informed consent. Forty-four patients were included, 22 in each treatment arm.

Quality of life interviews (see below) were performed either by a research nurse or by a psychologist at randomization and at the time of each response evaluation. The first interview is missing for two MFL patients. Patients who did not participate in the second, third, and so forth interviews had either died before the time of the interview or were treated terminally at their local hospital.

Sex, age distribution, site of disease, type of symptoms and KPS at the time of randomization are shown in Table 1. There were no significant differences (t-test) between the groups on any of these variables.

The interviews were conducted according to a structured questionnaire constructed for the present study. The interviewer posed each question to the patient who indicated his/her response on a questionnaire sheet. The questionnaire consisted of five parts: (1) *Pain* (last 14 days). The patient indicated pain location on a schematic drawing of the human body and intensity on a 0–10 scale, with 0 = very weak pain and 10 = intolerable pain. Three different locations could be rated. (2) *Symptoms and adverse treatment effects* (last 14 days). The patient indicated the occurrence of the following 25 different events: haemorrhagic expectorations, dyspnoea, diarrhoea, mucositis, complaints from the right side of the abdomen, conjunctivitis, headache, tiredness, irritation, crying, sleeping problems, loss of appetite, nausea, feeling sick, changed taste sensations, hair loss, anal or genital discharge, stomach pain, vomiting, heartburn, early satiety of meals, constipation, flatulence and pain. (3) *Frequency of troublesome events* (last 14 days). Here, the patient rated on a 4-step frequency scale how often certain everyday events occurred. The scale ranged from 'less than once a week' to 'several times per day'. The following events were rated: resting after physical performance, resting in general, crying, skipped meals, problems concentrating on tasks, consumption of analgesics

Table 1. *Age, sex, Karnofsky performance status (KPS), tumour sites and tumour symptoms at the time of randomization*

	5-FU	MFL
	Number of patients	
Included	22	22
Median age (range)	63 (40–74) years	61 (37–73) years
Male:female	11:11	11:11
KPS 100	6	4
80	11	8
60	5	10
Tumour site		
liver	16	17
lung	2	4
peritoneal	—	2
local	6	6
others	7	6
1 site only	13	10
2 or more sites	9	12
Type of symptoms		
pain	17	14
fatigue	10	14
weight loss/anorexia	8	7
GI bleeding/soiling	4	2
others	—	6
1 symptom only	9	7
2 symptoms	9	9
3 or more symptoms	4	6

and use of pads. (4) *Nausea and vomiting* (before, during and after the present course of treatment). These questions were not used in the interview performed at randomization. Patients rated the intensity of nausea (0–10 scale, with 0 = no nausea and 10 = strong nausea) and frequency of vomiting. They also indicated the development of food aversions after the start of treatment (yes/no). (5) *Tiredness and pain in association with everyday activities* (present situation). Patients rated the degree of tiredness and pain they thought they would experience after performing the following eveyday activities: Tiredness (scale: 0 = not tired at all to 10 = very tired); sitting for an hour, traveling by bus or car for an hour, walking for an hour; Pain (0 = no pain to 10 = strong pain): dressing, household activities, rising from a chair, going shopping, performing light work for an hour, at bedtime, after sitting with friends for an hour and walking for an hour.

The interviews lasted between 10 and 15 min and were very well tolerated by the patients, who often indicated that they found the experience valuable.

Statistical methods

Differences between groups were tested by independent two-sided *t*-tests in most cases. No adjustment was made for multiple comparisons. In some instances, analysis of variance (split-plot design) was employed to study between-group differences overtime. Survival was calculated using the life-table method described by Peto *et al.* [13] and differences were tested using the log-rank test.

RESULTS

Evaluation of response: physician's judgement

Objective responses and survival. In the MFL group, five patients had a PR and seven prolonged SD in contrast to only one PR and two SD in the FU-group (Table 2). The remaining patients had either short-lived stationary disease (SD/PD) or PD. The duration of the PRs ranged between 5 and 25 months (median 13) and the SDs between 6 and 21 months (median 9). Median time to progression was 6 months in the MFL group vs. 2 months in the 5-FU group. Total survival for patients randomized to MFL appeared superior to that for patients randomized to 5-FU with median survivals of 9 vs. 4 months (Fig. 1, log-rank test, $P = 0.1$).

Number of treatment courses. The number of treatment courses was lower in the 5-FU group (median 4, mean 5.5, range 1–28) than in the MFL group (median 10, mean 9.7, range 1–36). In both treatment groups, eight patients failed to obtain four treatment courses, in all instances because of rapid disease progression.

Nine of the patients randomized to 5-FU received MFL as second line treatment after failure to 5-FU. One of those patients received a PR and two SD while on MFL. None of the patients randomized to MFL were given 5-FU as second-line treatment.

Karnofsky performance status (KPS). There was no difference (*t*-test) between groups in KPS at randomization, but there was a stronger decline in the 5-FU group than in the MFL group over time (Fig. 2). Deceased patients were given a score of 0 at the evaluations after 4, 8 and 12 courses, respectively. Analysis of variance showed an interaction of groups with time ($P < 0.001$). A large part of this difference reflects differential mortality. Therefore, KPS values for living patients only are plotted separately; the data illustrated a slight increase of KPS in the MFL group and virtually no change in the 5-FU group.

All patients with PR or SD had either an increase of KPS (nine cases) or an unchanged KPS (six cases, three of which had KPS = 100 at the start) over a 4–5 month period.

Subjective responses. In the MFL group, 12 of the 22 patients were considered free from any tumour related symptoms or improved at one or more evaluations (Table 2). In the 5-FU group, only five

Table 2. Objective and subjective responses according to treatment as judged by the physician

Treatment	Objective response	Subjective response				Total
		Symptom-free	Improved	Unchanged	Worse	
		(number of patients)				
MFL	PR	4	—	1	—	5
	SD	6	1	—	—	7
	SD/PD	—	1	—	—	1
	PD	—	—	1	8	9
	Total	10	2	2	8	22
5-FU	PR	1	—	—	—	1
	SD	2	—	—	—	2
	SD/PD	—	2	1	1	4
	PD	—	—	3	12	15
	Total	3	2	4	13	22

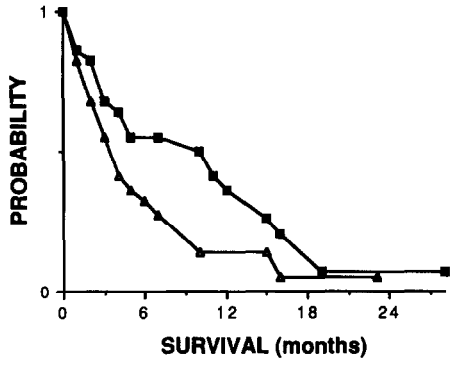

Fig. 1. Probability of survival in patients randomized to MFL (■—■, n = 22) or to 5-FU (△—△, n = 22). The difference is statistically insignificant (P = 0.1, log-rank test).

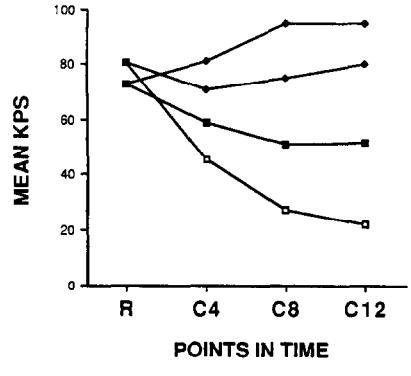

Fig. 2. Mean Karnofsky performance status (KPS) at randomization (R) and after treatment course 4 (C4), 8 (C8) and 12 (C12), respectively, in all patients randomized to MFL or 5-FU. Computations are based on total groups (MFL ■; 5-FU □) (P < 0.001, split-plot design) and on patients alive at the respective points in time (MFL ◆; 5-FU ◇).

Table 3. Acute and subacute toxicity after cytostatic treatment

	Patients with toxicity grade*				
	0	1	2	3	4
MFL group					
Leukopenia	22	†	0	0	0
GI toxicity:					
nausea/vomiting	13	7	2	0	0
stomatitis/diarrhoea	21	0	1	0	0
Conjunctivitis	17	5	0	0	0
Hair loss	21	1	0	0	0
5-FU group					
Leukopenia	20	†	1	1	0
GI toxicity:					
nausea/vomiting	14	3	5	0	0
stomatitis/diarrhoea	20	1	1	0	0
Conjunctivitis	22	0	0	0	0
Hair loss	22	0	0	0	0

*WHO: recommendations for grading of acute and subacute toxic effects.
†Not registered as toxicity.

patients became symptom free or improved. All patients but one with PR or SD improved or became symptom free.

Adverse treatment effects. Both regimens were well tolerated with only minor adverse effects (Table 3). The most frequent adverse effect was nausea/mild transient vomiting. There was no renal toxicity. Besides conjunctivitis, there was no difference in the number and severity of physician reported adverse events between the two treatments, in spite of the fact that more courses were delivered to the MFL patients.

'Quality of life': patient's judgement

Since the number of patients in the 5-FU group diminished more rapidly than in the MFL group, data from interviews performed at or later than treatment course 8 (C8) are based on four patients or less in the 5-FU group. Therefore, for most measures, statistical comparisons are restricted to the interviews performed at randomization (R) and after four treatment courses (C4).

Table 4. The total number of symptoms and adverse effects reported by patients at randomization (R) and after course 4 (C4)

	R	C4	Improved*	New*
MFL group	67	54	51	34†
5-FU	68	83	33	48

*Improved = the total number of symptoms and effects at R but not at C4. New = the total number of symptoms and effects not reported at R but at C4.
†Nine of these were conjunctivitis.

Pain. Very few patients reported more than one pain site. Mean pain intensity changed from 3.5 to 1.7 ($n = 12$) in the MFL group and from 5.2 to 3.2 ($n = 13$) in the 5-FU group between R and at C4. Analysis of variance showed a significant decrease over time ($P < 0.05$), but there was no significant difference between the groups.

Symptoms and adverse treatment effects. The total number of reported symptoms and adverse treatments effects at R and C4 are shown in Table 4. After an approximately equal number of reports at R, the total number increased by 15 in the 5-FU group, whereas it decreased by 13 in the MFL group. With the exception of conjunctivitis, the reports are fairly equally distributed between groups. Conjunctivitis was reported by no patient at R, but by one 5-FU patient and by nine MFL patients at C4.

Frequency of troublesome events. There was no difference between the groups at R. At C4, the mean frequency of the listed events was 1.8 in the MFL group ($n = 14$) and 2.4 in the 5-FU group ($n = 13$, $P < 0.05$). For individual events, the 5-FU patients had skipped a meal more often than the MFL patients (1.9 vs. 1.1, $P < 0.05$).

Nausea and vomiting. At C4, patients from both groups reported the same degree of nausea and vomiting. At C8, mean nausea intensity (computed across values given before, during and after treatment) was higher in the 5-FU group (4.0, $n = 4$) than in the MFL group (1.1, $n = 12$, $P < 0.05$). The 5-FU patients also reported more nausea before (means 3.3 vs. 0.9, $P = 0.07$) and after (4.8 vs. 1.2, $P < 0.02$) treatment, when these time points were considered separately.

Tiredness and pain in everyday activities. There were no between-group differences at R. At C4, patients in the 5-FU group ($n = 13$) reported a higher mean tiredness/pain value (4.4) than those in the MFL group (2.1, $n = 14$, $P < 0.05$). On individual items, the 5-FU group was more tired after sitting with others for an hour (means 5.7 vs. 2.5, $P < 0.05$) and after riding a bus or a car for an hour (means 4.2 vs. 1.8, $P < 0.05$) as compared to the MFL group. The 5-FU group also reported more pain than the MFL group after shopping (6.4 vs. 1.7, $P < 0.01$) and possibly also after performing household activities (4.6 vs. 2.0, $P = 0.08$).

Changes in 'quality of life' during treatment: physician's and patient's judgement

Based upon the ratings made by the physician and those presented by the patient in the interview, the patients were categorized according to whether they had improved their 'quality of life' during treatment or whether it remained unchanged or became worse. The duration of any improvement was calculated as from the date of randomization to the date of any worsening.

The information provided by the physician was changes in KPS and tumour related symptoms and magnitude of adverse effects. In no instance were the adverse effects considered severe (besides the single patient with LPK 0.9, who did not notice this) by the physician.

The information provided from the patient was the mean of the scores in the five parts of the questionnaire (see above). A patient who was interviewed only at R was considered 'not improved', since they all had rapidly progressive disease and/or early death from disease.

The judgement of whether a patient had improved his/her 'quality of life' or not was made by two referees independently and separately for the information provided by the physician and the patient and without knowledge of whether the patient belonged to the MFL group or the 5-FU group. Details of this procedure will be published elsewhere, but the correlation between the two referees was high for both the patient's and the physician's opinions (product moment correlation = 0.9). In the few cases of disparate opinion (one case physician, three cases patient), a joint decision was made.

In the MFL group, 12 (55%) patients were considered improved based upon both the information provided by the physician and by the patient (Table 5). The two patients who did not have an interview at randomization, and thus were not fully evaluable, were both improved and remained so for a prolonged time period. There was a discordance between the patient's and the physician's opinion for two patients. One of the discordant patients had several and severe symptoms, both from disease and from complications related to previous surgery, at randomization. The clear improvement in tumour related symptoms and in KPS, as recorded by the physician, was not detected by the referees, probably because of several, but mild, adverse effects.

Table 5. Changes in 'quality of life' during treatment as judged by the physician and by the patient

Treatment group	Physician's judgement	Patient's judgement: Improved	Patient's judgement: Unchanged/worse	Total
		Number of patients (percentage)		
MFL	Improved	11	1	12 (55)
	Unchanged/worse	1	9	10
	Total	12 (55)	10	22
5-FU	Improved	2	3	5 (23)
	Unchanged/worse	—	17	17
	Total	2 (9)	20	22

In the 5-FU group, only two (9%) patients had an improvement according to their own opinion, whereas the physicians claimed that five (23%) patients were improved. Two of the discrepancies were in patients where the physician recorded short-lived symptom improvement with only mild–moderate adverse effects. From the interviews, it was apparent that one of the patients had a definite symptom improvement but relatively marked adverse effects. That patient was the only one where the adverse treatment effects influenced the 'quality of life' estimation. The second patient described that she was marginally improved in the questionnaire which was not recorded by the referee. The third discrepancy was in a patient with only minor pain at randomization, where the doctor, but not the patient, recorded some pain relief.

The duration of the improvements in 'quality of life' lasted between 2 and 25 months (median 8 months) in the MFL group and between 2 and 21 months (median 4 months) in the 5-FU group.

DISCUSSION

The present data indicate that MFL is superior to 5-FU as a palliative treatment of patients with symptomatic colorectal cancer. This superiority is demonstrated by a variety of indices of 'quality of life' reported by the patients. It is, however, also shown with respect to objective and subjective responses and changes in KPS, as judged by the physician, and by survival. It should be remembered that the number of patients in this trial is small, so the generality of the results may be questioned. However, the data are confirmed in the Nordic trial including 249 patients where the magnitude of objective responses (MFL 24%, 5-FU 3% of patients evaluable for objective response, respectively, $P < 0.001$), subjective responses (MFL 45%, 5-FU 23%, $P < 0.001$), survival (median 9 months vs. 6 months, log-rank test $P < 0.02$), changes of KPS and the number of treatment courses given to each treatment group was the same as in the present study (data to be published). We therefore believe that the present results are representative of the larger trial and that general conclusions can be drawn.

Although 5-FU has been used extensively for decades, the extent to which this therapy relieves the symptomatic patient of symptoms and improves 'quality of life' has not been properly investigated. The present data indicate that not more than 10 to 20% of the patients will improve for a short time period. The objective response rate (5%, 1/22) is perhaps lower than usually recorded [1–4], but it should be remembered that, in this study, all patients were symptomatic.

The beneficial effect was strongly correlated to whether the tumour related symptoms were improved or not. In only one instance, a patient in the 5-FU group with a short symptomatic improvement, did the adverse effects of treatment negatively influence the patient's 'quality of life'. Both the MFL regimen and 5-FU were well tolerated as judged by the physician, using conventional WHO criteria, and by the patients. However, it should be noted that patients revealed more cases with conjunctivitis and nausea/vomiting than the physicians did. The results also show that patients who obtain an objective response as well as those with a prolonged SD are subjectively improved.

The data indicated a good overall agreement between the judgements by the physician and the patient, particularly with respect to symptoms but also adverse treatment effects. This suggests that the prospective recording of 'subjective responses' by the physicians in the Nordic trial may possess an adequate degree of validity.

The 'quality of life' instruments employed were constructed especially for the present study. They were based on the premise that the best way to investigate how cancer and its treatment affect patients' 'quality of life' is to anchor the questions in everyday activities. Also, those items that best differentiated between the treatment groups were those concerned with changes in everyday activities.

In conclusion, a combination of sequential methotrexate and 5-FU followed by conventional leucovo-

rin rescue (MFL) appears superior to 5-FU alone as palliative treatment in this randomized comparison evaluating the 'quality of life' during treatment of advanced symptomatic colorectal cancer. Using MFL, about 50% of the patients will experience improved 'quality of life' with a median duration of 8 months.

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