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Specialist Interest Articles

Sequential 5-fluorouracil and Leucovorin in Patients with Advanced Symptomatic Gastrointestinal Cancer

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50 patients with advanced symptomatic gastrointestinal cancer were treated with sequential 5-fluorouracil (5-FU)/leucovorin. Patients received an intravenous bolus injection of 5-FU (500 or 600 mg/m^2) and leucovorin 30–40 min later, either 50 mg (41 patients) or 200 mg (9 patients). Treatment was given in repeated courses either once weekly or on 2 consecutive days every other week until progression. Toxicity was mild with the lower leucovorin dose, although grade 2 toxicity, particularly diarrhoea, occurred in 27 (66%) patients. All patients receiving the higher leucovorin dose had grade 2–4 toxicity. Toxicity was less with the lower 5-FU dose. Out of 40 patients with colorectal cancer, 34 received leucovorin 50 mg and 6 received 200 mg. Partial response occurred in 10 (29%) and 1 of these patients, respectively. This sequential 5-FU and intermediate-dose leucovorin regimen has acceptable toxicity and a definite anti-tumour activity.
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INTRODUCTION

CHEMOTHERAPY IS extensively used for palliation in patients with advanced colorectal cancer. 5-fluorouracil (5-FU) has been widely used, either alone or in combination with other drugs such as leucovorin or methotrexate. In controlled studies, response rates were 20–30% [1–4]. The combination of 5-FU and leucovorin has attracted interest despite gastrointestinal toxicity [2, 5, 6]. Schedules and doses have varied considerably. Experimental findings and pharmacodynamic studies of 5-FU and leucovorin in patients' tumour tissues indicate a rationale for sequential bolus administration to optimize the antitumour effect [7–9]. An improved antitumour effect may be obtained if 5-FU precedes the leucovorin injection by approximately 40 min. Our aim was to assess toxicity and response with such sequential administration in patients with advanced symptomatic colorectal cancer.

PATIENTS AND METHODS

Patients (*Table* 1)

40 patients, average age 61, with a histologically verified and symptomatic non-curable colorectal cancer were included. All patients had measurable disease. Primary tumour location was colon in 29 patients and rectum in 11. 33 patients had not previously received chemotherapy and 7 patients had previously been treated with sequential methotrexate/5-FU and leucovorin [3]. The average Karnofsky performance status was 70 (range 40–90) at the start of treatment. The tumour location was liver only in 11 patients, lymph nodes only in 3 patients and local tumour growth only in 2 patients while the remaining 24 patients had multiple sites of tumour growth. In 18 patients (45%) the liver was involved whereas 6 patients (15%) had tumour growth in the lung and other sites excluding the liver. 21 patients had

Table 1. *Patients' characteristics**

	Leucovorin (mg)/5-FU (mg/m^2)		
	50/500	50/600	200/500
M/F	7/10	10/14	4/5
Age	62 (36–78)	61 (40–74)	65 (56–78)
Cancer			
Colorectal	15	19	6
Other	2	5	3
Mean Karnofsky index	70 (40–90)	70 (50–90)	80 (70–90)
Treatment period (weeks)	13 (2–54)	17 (3–41)	16 (7–48)
Symptoms			
Pain only	5	14	5
Multiple	12	10	4
Previous chemotherapy	2	4	2
Single tumour sites			
Liver	6	6	1
Nodes	2	1	—
Local	4	1	—
Multiple tumour sites			
Liver included	4	13	5
Liver excluded	1	3	3

*Number or mean (range).

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pain only (52%), while 19 patients (48%) had pain with other symptoms such as nausea, fatigue, ulceration or soiling.

In addition, 10 other patients, all with advanced cancer, were included in evaluation of toxicity. In this group the average age was 68 years (59–73) and the average Karnofsky performance status was 70 (50–90). The primary tumour was gastric in 2 patients, pancreatic in 3, breast in 2 and hepatocellular carcinoma in 3.

Treatment

All patients were treated between September 1987 and November 1988. The treatment was administered either once weekly (Göteborg) or on 2 consecutive days every other week (Uppsala). The patients had an intravenous bolus injection of 5-FU followed 30–40 min later by leucovorin (intravenous bolus injection). The starting dose of 5-FU was 600 mg/m^2. The 5-FU dose could be lowered by 50–100 mg/m^2 if grade 3–4 toxicity or persistent grade 2 toxicity occurred. Because of toxicity the 5-FU starting dose was lowered to 500 mg/m^2 in the later part of the study. The first 41 patients received a total dose of 50 mg leucovorin while the final 9 patients received 200 mg. The evaluation of toxicity followed WHO guidelines and tumour response was assessed according to the UICC recommendations. Symptomatic response was recorded as described [3]. Response was evaluated every 8 weeks. Treatment was continued until progression of disease or severe adverse effects.

RESULTS

Toxicity

In the 41 patients who had a leucovorin dose of 50 mg the average treatment period was 15 weeks (2–44). The average time to toxicity was 6 weeks (1–25). Toxicity occurred in 17 out of 24 patients (71%) with a 5-FU starting dose of 600 mg/m^2, compared with 10/17 patients (59%) with a 5-FU starting dose of 500 mg/m^2 ($P = 0.6$, χ^2 test) (Table 2). The 5-FU dose had to be reduced because of toxicity in 9 (38%) patients who started 5-FU at 600 mg/m^2 compared with 3 (18%) who started at the lower dose ($P = 0.3$). No patients who received leucovorin 50 mg stopped treatment because of toxicity.

Table 2. Number of patients with toxicity due to treatment

	Leucovorin (mg)/5-FU (mg/m^2)		
	50/500 (n = 17)	50/600 (n = 24)	200/500 (n = 9)
Diarrhoea			
2*	0	10 (42%)	5 (56%)
3–4	0	1 (4%)	4 (44%)
Stomatitis			
2	0	5 (21%)	3 (33%)
3–4	0	0	1 (11%)
Nausea/vomiting			
2	5 (29%)	4 (17%)	6 (67%)
3–4	0	0	1 (11%)
Conjunctivitis			
2	3 (18%)	3 (13%)	2 (22%)
3–4	0	0	0
Granulocytopenia			
2	2 (12%)	0	0
3–4	0	1 (4%)	0

*Grade.

Table 3. Objective tumour response

	Leucovorin	
	50 mg (n = 34)	200 mg (n = 6)
Complete response	0	0
Partial response	10 (29%)	1 (17%)
Stable disease	10 (29%)	2 (33%)
Progressive disease	14 (41%)	3 (50%)

Table 4. Subjective responses in relation to objective tumour response

	Free	Diminished	Unchanged	Increased	Total
Partial response	6 (55%)	5 (45%)	0	0	11 (28%)
Stable disease	0	8 (67%)	4 (33%)	0	12 (30%)
Progressive disease	0	0	9 (53%)	8 (47%)	17 (42%)
Total	6 (15%)	13 (33%)	13 (33%)	8 (20%)	40 (100%)

Among the 9 patients who received leucovorin 200 mg, grade 2–4 toxicity, predominantly diarrhoea, was observed in all patients despite a 5-FU starting dose of 500 mg/m^2 (Table 2). The average treatment time was 12 weeks (2–48) and the mean time to toxicity was 4 weeks (1–6). The 5-FU dose had to be reduced because of toxicity in all patients. Interruption of the schedule was necessary in 4 inpatients with severe diarrhoea. The difference between the groups treated with leucovorin 50 mg and 200 mg as regards toxicity that required 5-FU dose reduction was significant ($P = 0.0004$).

Tumour response

40 patients with colorectal cancer were evaluated for tumour response (Table 3). No complete response was noted. 10 out of 34 patients treated with leucovorin 50 mg had a partial response. In 1 patient out of 6 treated with leucovorin 200 mg, a partial response was observed. The mean response duration was 7 months (6–11). 2 out of 7 patients (29%) previously treated with chemotherapy responded compared with 9 of 33 untreated patients (27%). The response rate was similar if the treatment was administered once a week or on 2 consecutive days every other week.

Subjective responses were also assessed (Table 4). Those patients with a partial tumour response or with stable disease had improvement of symptoms to a greater extent than patients with progressive disease ($P < 0.0001$).

DISCUSSION

The rationale for our sequential administration of 5-FU and leucovorin was based on measurements of intratumoral peak concentration of 5-fluorodeoxyuridine monophosphate (FdUMP), which is achieved 30–60 min after intravenous bolus injection of 5-FU, while the peak concentration of the thymidylate synthetase cofactor CH_2FH_4 is achieved 10–15 min after intravenous bolus injection of leucovorin [8]. To achieve simultaneous peak concentrations of FdUMP and the cofactor after intravenous bolus administration, 5-FU should precede leucovo-

rin by about 40 min. In an experimental tumour model in rats, 5-FU administered 40 min before leucovorin was more efficient than simultaneous administration in reducing hepatic tumour growth. Administration of leucovorin 1 h before 5-FU induced no synergism [9].

Leucovorin dose was correlated with toxicity in our study. The higher leucovorin dose caused toxicity that required either treatment interruption or dose reductions in all patients. Because of the limited number of patients it is not known whether this sequential approach with 5-FU preceeding leucovorin at 200 mg causes more toxicity than protocols with leucovorin preceeding 5-FU. In the patients with a 5-FU starting dose of 600 mg/m^2 plus the lower leucovorin dose, subjective toxicity of grade 2 or 3 (usually stomatitis, conjunctivitis and diarrhoea) was frequent. Since the treatment was palliative, toxicity should be low. Therefore, it was felt justified to lower the 5-FU dose to 500 mg/m^2. We think that 5-FU 500 mg/m^2 followed by leucovorin 50 mg, as a weekly schedule or given every other week on 2 consecutive days, has acceptable toxicity considering that it is palliative with probably no major survival benefit.

A palliative treatment should not only have acceptable toxicity but also antitumour activity. In our study, the objective response findings and the proportion of patients subjectively improved were about the same as those reported after combinations of 5-FU and leucovorin [1, 2, 4] or sequential methotrexate/5-FU/leucovorin [3]. Whether there are differences in antitumour activity between the 5-FU doses cannot be judged from our study because of the limited number of patients and the absence of random selection.

This sequential 5-FU/leucovorin schedule requires further clinical evaluation since the combination has clinical activity with acceptable toxicity. We are testing two daily doses every second week against sequential methotrexate, 5-FU and leucovorin and 5-FU in a multicentre phase III trial.

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Biodegradable Emboli and Antibody Targetting of Colorectal and Gastric Hepatic Metastases: A Pilot Study

William H. Allum, Alan J. Jewkes, Elsie Lanchbury, Steven Darby, Fiona Macdonald and Terry O'Brien

The effect of degradable starch microspheres (DSM) on the passage of a low molecular weight marker through the liver of patients with metastases was compared with the passage of an anti-carcinoembryonic antigen monoclonal antibody. In all six patients studied DSM reduced the passage of the marker into the systemic circulation. In three patients who received labelled whole antibody, DSM had no effect. In two of three who received antibody fragments a similar delay to the low molecular weight marker was observed. This delay is likely to be a result of the smaller size of the fragments and may represent accumulation within the extravascular space.

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