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High-dose Folinic Acid (HDFA) Combined with 5-Fluorouracil (5-FU) in First Line Chemotherapy of Advanced Large Bowel Cancer

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Abstract—*The therapeutic activity of 5-FU in large bowel cancer is enhanced by increasing the intracellular pool of reduced folates. We treated 45 patients with advanced colon cancer with HDFA and 5-FU for 5 consecutive days. None had been given previous radio- or chemotherapy. All had measurable disease. Not one complete response was observed. Thirteen of the 39 evaluable patients showed partial response. Median duration of response was 9+ months. The probability of 50% survival was 15 months for all evaluable patients. There was no case of severe toxicity and the principal toxic effects were oral mucositis and diarrhea.*

To date, HDFA + 5-FU is one of the most effective treatments for large bowel cancer.

INTRODUCTION

5-FLUOROURACIL (5-FU), the most active agent in treatment of colorectal cancer [1], remains inactive until converted into its nucleotide derivatives. One of these, fluorodeoxyuridilate (FdUMP), inhibits the enzyme thymidylate synthetase (TS) thus suppressing DNA synthesis [2, 3]. Administration of high-dose folinic acid (HDFA) may increase the intracellular pool of reduced folates and enhance 5-FU cytotoxicity [4, 5].

In 1982, Machover *et al.* presented the results of the first pilot trial on treatment of advanced colorectal cancer with 5-FU + HDFA [6]. Our preliminary data were presented at ECCO 3 in June 1985 [7]. This paper reports the results 3 years after the beginning of our study.

PATIENTS AND METHODS

Between September 1983 and June 1986, 45 patients were considered. All had histologically proven metastatic large bowel cancer. Patients previously given radio- or chemotherapy and those with rectal adenocarcinoma were excluded.

The eligibility criteria were: measurable disease; performance status (ECOG) < 2; survival expectancy > 1 month; hematological, renal, hepatic and cardiac function normal apart from changes resulting from direct tumor invasion; no previous malignancy. Liver lesions were measured by echography and/or CT scan [8]. Serosal effusions were not considered as measurable disease. Informed consent was obtained from all patients. Table 1 shows the breakdown on patients.

Table 1. Patients' data

Entered	45
Evaluable	39
Mean age (range)	57 (31–73)
Male/female	29/10
Performance status	
0	20
1	12
2	7
Primary tumor not resected	6
Site of tumor involvement	
Liver	13
Lung	3
Liver + lung	9
Abdominal	14

Treatment consisted of 5-days courses of HDFA (200 mg/m^2/day by intravenous bolus) + 5-FU (370 mg/m^2/day by intravenous infusion over 15 min) followed by drug free intervals of 23 days.

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Table 2. Response to therapy according to performance status and site of tumor involvement

	No. of patients		
	PR	SD	PD
Performance status			
0	7	9	4
1	2	3	7
2	4	1	2
Site of tumor			
Liver	4	6	3
Lung	2	—	1
Liver + lung	3	2	4
Abdominal	4	5	5
Total	13	13	13

When WHO grade 3 or 4 oral mucositis or diarrhea occurred, the daily dose of 5-FU was reduced by 30 mg/m^2/day. If the leukocyte count was below 3700/mm^3 and/or the platelet below 100,000/mm^3 treatment was delayed. Courses of treatment were repeated until there was progression.

Patients were considered evaluable for response after at least two courses of chemotherapy. Responses were normally assessed at the beginning of the fourth cycle. Partial responses of less than 3 months were not considered.

Standard WHO criteria were used to evaluate the objective response: complete response (CR); partial response (PR); stable disease (SD); progressive disease (PD) [8].

The treatment was given to outpatients. Survival was calculated from the first day of treatment. Time to disease progression was from the beginning of chemotherapy to the date on which progression was first observed. The graph was made using the Kaplan and Meier method [9].

RESULTS

Six of the 45 patients considered were excluded because they were lost to follow up after the first treatment cycle. Not one of the remaining patients had a CR, and 13 had a PR (response rate 33%). The duration of remission in the PR group was 9+ months (range 4+ to 18). Median survival for the 39 evaluable patients was 10+ months. Table 2 shows response to therapy according to performance status and metastatic site. Tumor mass and diffusion were used to distinguish two subgroups: limited metastatic disease (less than five lesions, each with a largest diameter of 3 cm) and widespread metastatic disease (over 5 lesions or one larger than 3 cm). Nine PRs were observed in 21 patients with limited disease, but only four among the 18 patients with widespread disease (Table 3). The difference is not statistically significant.

Toxicity was assessed in 41 patients and 250 cycles of chemotherapy (Table 4). Major side effects were grade 2 + 3 WHO diarrhea and oral mucositis. Hematological toxicity was very mild. Two patients developed grade 2 alopecia. Life-threatening complications never occurred.

Table 3. Response to therapy according to tumor burden

	No. of patients		
	PR	SD	PD
Limited disease	9	9	3
Widespread disease	4	4	10
Total	13	13	13

Table 4. Overall toxicity in 250 cycles of chemotherapy with HDFA + 5-FU

	% of cycles				
WHO grading	0	1	2	3	4
Nausea	73	24	3	—	—
Oral mucositis	33	40	18	9	—
Diarrhea	55	14	20	1	—
Anemia	86	12	2	—	—
Leukocytes	92	4	3	1	—
Platelets	98	1	1	—	—
Cutaneous	77	13	8	2	—

Table 5. Survival in patients with untreated liver metastases

Reference	Extent of involvement	Survival
Bengmark and Halfstrom [10]	Few solitary	4% 1 year
	Widespread	2% 1 year
Nielsen *et al.* [11]	Few	18 months
	Several	9 months
	Multiple	5 months
Jaffe *et al.* [12]	Solitary	4–5 months
	One lobe	3–1 months
	Widespread	2–8 months
Bengtsson *et al.* [13]	< 25%	6.2 months
	25–75%	5.5 months
	> 75%	3.4 months
Wood *et al.* [14]	One lobe	27% 1 year
	Widespread	5–7% 1 year

DISCUSSION

In advanced colorectal cancer with only liver metastases the median survival time is generally reported as approx. 6 months from diagnosis. Virtually all patients with untreated metastatic disease were dead within 2 years of diagnosis (Table 5). The median duration of response observed in our patients was 9+ months. Tumor burden was the most important prognostic factor. If only those patients with limited metastatic disease are con-

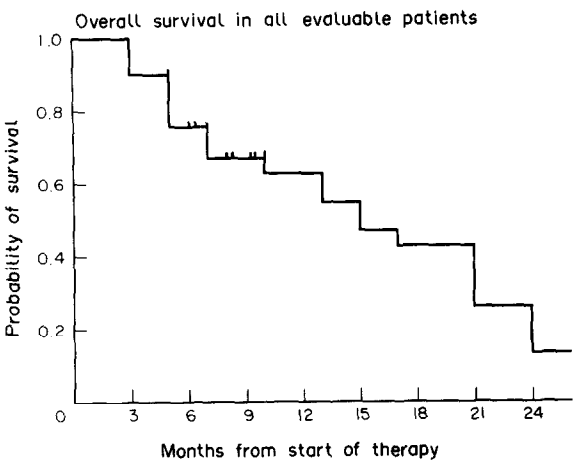

Fig. 1. Overall survival in all evaluable patients.

sidered, the PR rate rises from 33% to 43% (9/21 cases).

Following Anderson and Davis [15, 16], we report only the overall survival of the entire group of evaluable patients which was 10+ months (Fig. 1). The probability of 50% survival was 15 months (S.E. 0.09) [17]. When the historical survivals reported in Table 5 are taken into consideration, this duration appears remarkably long.

Our results confirm the activity of HDFA + 5-FU reported by Machover *et al.* and subsequently by other authors using the same schedule [6, 18–21] or a weekly administration regime [22, 23].

We found HDFA + 5-FU considerably more toxic than 5-FU alone at the same dose. Of 23 patients treated with 5-FU (375 mg/m^2 day i.v. for 5 days) + CCNU only 10% developed mucositis and diarrhea [24]. Despite its toxicity, HDFA + 5-FU remains one of the most effective treatments for advanced large bowel cancer. Since this association is virtually a monochemotherapy, we do not believe it will be possible to obtain a response rate greater than 30–40% in chemoresistant tumors such as colon cancer [25].

To improve on these results further studies are needed with other active drugs. The enhancement of 5-FU cytotoxicity by HDFA should, however, be tested in tumors in which 5-FU shows some therapeutic activity.

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