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Acknowledgements—We thank Deborah Tsuji for help with data collection and Brigitte Caplan for technical support. Part of the study was supported by a grant from Direktør Ib Henriksens Fond.

Eur J Cancer, Vol. 26, No. 10, pp. 1054–1056, 1990.
Printed in Great Britain

0277-5379/90 $3.00 + 0.00

Folinic Acid plus High-dose 5-fluorouracil with Allopurinol Protection in the Treatment of Advanced Colorectal Carcinoma

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Protection by prolonged administration of allopurinol against high-dose 5-fluorouracil (5-FU) administered with folinic acid in 74 patients with colorectal cancer was investigated. The dose of 5-FU was 700 mg/m^2 per day for 5 days. Of 41 patients without previous chemotherapy, 1 had a complete response and 4 had partial responses (total 12%), 15 remained stable and 21 progressed. Mean duration of response was 7.4 (1.8–12.6) months. The most frequent toxicities were decreased granulocytes (13%), diarrhoea (37%), and stomatitis (35%), which were similar to the frequencies of other studies with lower doses of 5-FU without allopurinol. Prolonged administration of allopurinol thus gives some protection to patients with colorectal cancer who receive folinic acid plus high-dose 5-FU but responses were not better than those with conventional doses.
Eur J Cancer, Vol. 26, No. 10, pp. 1054–1056, 1990.

INTRODUCTION

FOLINIC ACID pretreatment enhances 5-fluorouracil 5-FU efficacy and toxicity by an interesting biochemical mechanism. The folinic acid metabolite, 5,10-methylenetetrahydrofolate, tightly binds the active 5-FU metabolite, fluorodeoxuridine monophosphate (FdUMP), to thymidylate synthetase, inactivating the enzyme completely and shutting down *de novo* thymidilate synthesis [1].

Early trials of folinic acid plus 5-FU in patients with metastatic colon cancer were reported in 1982, with responses in patients with cancers refractory to 5-FU and improved responsiveness over that expected with 5-FU alone in previously untreated patients [1, 2]. Toxicity was substantial (neutropenia, diarrhoea, stomatitis and neurological symptoms). Many institutions have tested folinic acid and 5-FU combinations with similar results [3, 4].

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We have tried to obtain a sufficient response with low and acceptable toxicity by using an ordinary dose of folinic acid with high-dose 5-FU. In addition, for more protection, we added allopurinol because metabolites of allopurinol were expected to inhibit 5-FU catabolism by orotidine phosphorybosyl transferase in normal tissues but not in tumour tissues [5, 6]. There are, however, doubts about the efficacy of this combination [7, 8], although our previous work [9] showed some protection by allopurinol. There are no comparative or randomised studies [10].

PATIENTS AND METHODS

Between June 1987 and September 1989, 74 patients with advanced colon cancer, mean age 61, entered the study (Table 1). Eligibility criteria included: (1) biopsy-proven adenocarcinoma of the colon or rectum; (2) measurable metastatic disease; (3) Karnofsky status of 60 or better, with life expectancy of at least 2 months; and (4) no brain metastases.

The treatment schedule was as follows. Allopurinol 300 mg, three times per day orally was given for 17 days starting 2 days

Table 1. Details of 74 patients with advanced colorectal cancer

	Number
Age	
< 50	9
50–65	33
> 65	32
M/F	46/28
Karnofsky status	
100	4
90	15
80	19
70	22
60	14
Primary site	
Colon	19
Sigmoid	37
Rectum	18
Site of metastases	
Liver	52
Abdomen	16
Pelvis	43
Lung	16
Lymph nodes	30
Bone	5
Other	6
Previous therapy	
None	41
Radiotherapy	16
Chemotherapy	17*
Transfusions during therapy	16

* 5-FU with or without mitomycin C.

Table 2. Effect of treatment

	Response	No.
Total response	CR	2 (3%)
	PR	7 (9%)
	SD	24 (32%)
	PD	41 (55%)
No previous chemotherapy or radiotherapy	CR	1 (2%)
	PR	4 (10%)
	SD	15 (36%)
	PD	21 (51%)
Previous radiotherapy	CR	0 —
	PR	1 (6%)
	SD	7 (44%)
	PD	8 (50%)
Previous chemotherapy	CR	1 (6%)
	PR	2 (12%)
	SD	2 (12%)
	PD	12 (70%)

before the other drugs. Folinic acid 200 mg/m^2 per day was given by intravenous infusion before 5-FU infusion 700 mg/m^2 per day in 500 ml 5% dextrose water over 1 h for 5 days. The cycle was repeated every 21 days. The dose of folinic acid remained constant, but the dose of 5-FU was increased or decreased according to toxicity, with a 10% dose increment if there was no toxicity. A 10–20% dose decrement of 5-FU was used on the first cycle and in the event of grade 2–3 myelosuppression or grade 3 mucositis.

Patients had weekly blood counts and physical examination. Serum biochemistry was assessed every 3 weeks. Ultrasonic or computed tomographic (CT) scans were repeated every 9 and 18 weeks, respectively, to observe bidimensionally measurable lesions. Lesions visible on chest X-ray were evaluated every 6 weeks. A 50% or more decrease in the sum of the products of the perpendicular diameters of measurable lesions was defined as a partial response (PR), with the complete disappearance of all increased tumour markers and clinically evaluable disease constituting a complete response (CR). A 0–50% decrease was defined as stable disease (SD). Toxicity was estimated according to WHO criteria [11].

Statistical evaluation was based on χ^2 and Fisher's exact tests.

RESULTS

The patients received 326 courses of chemotherapy. We achieved a small escalation of doses, so the mean daily dose of 5-FU was 727.04 mg/m^2 (range 611–893), with a starting mean dose of 697 mg/m^2 (611–750) and a highest mean dose of 760.35 mg/m^2 (666–893).

The response rate, and its correlation with previous chemotherapy, is shown in Table 2. The overall response rate (CR plus PR) was 12%. The proportion of responders in patients who had not had previous chemotherapy or radiotherapy was 10%, and 6% in those who had had radiotherapy and 18% in those who had had previous chemotherapy. The patients who had had blood transfusion showed a lower response rate (86%/[S.D. 13%]) than the others ($P < 0.1$).

The mean duration of response was 7.4 (1.8–12.6) months and the mean time to progression was 6.8 (1.6–30.6) months. There was no significant difference between patients who had or had not received previous radiotherapy or chemotherapy in survival and time to progression.

Toxicity was estimated according to the number of therapy courses (Table 3). 5 patients in 9 cycles had tachycardia (6 cycles) and angina (3 cycles). Neurotoxicity included persistent headache, vertigo, fine tremor and, in elderly patients, restlessness and insomnia. Alopecia was limited (14 patients). 13 patients had dermatitis and 5 had hyperpigmented skin, especially in areas exposed to the sun. 36 patients had hyperpigmentation around the vein used for drug infusion.

DISCUSSION

We have confirmed that folinic acid plus 5-FU is active in the treatment of metastatic colon cancer. We also confirmed our previous experience [9] that prolonged administration of allopurinol protects against toxicity to allow higher doses of 5-FU to be administered in comparison to other similar studies [12–17]. Comparison with historical controls is of limited value, especially for toxicity. However, with the design of our study, this was the only comparison possible.

Other studies have reported the advantages of the traditional 5-FU loading dose and the more easily regulated toxicity obtained with a once a week schedule. We compared our schedule of once a day infusion of 5-FU for 5 days with those of other studies of combined 5-FU and folinic acid in colorectal carcinoma patients [12–19]. We used the same dose of folinic acid, about double the dose of 5-FU, and a shorter interval between cycles to obtain the same response and toxicity in patients previously treated or not with chemotherapy.

We found that extensive liver metastases were associated with

Table 3. Toxicity over 326 cycles

	WHO grade	No. of cycles	%
White cells	1	21	(6.4%)
	2	9	(2.8%)
Granulocytes	1	284	(87.1%)
	2	11	(3.4%)
	3	21	(6.4%)
	4	10	(3.1%)
Platelets	1	9	(2.8%)
	2	1	(0.3%)
Stomatitis	1	49	(15.0%)
	2	57	(17.5%)
	3	10	(3.1%)
Other mucositis	1	19	(5.8%)
	2	23	(7.1%)
	3	3	(0.9%)
Nausea/vomiting	1	20	(6.1%)
	2	11	(3.4%)
	3	1	(0.3%)
Diarrhoea	1	48	(14.7%)
	2	56	(17.2%)
	3	15	(4.6%)
Anorexia	1	58	(17.8%)
	2	57	(17.5%)
	3	9	(2.8%)
Weakness	1	61	(18.7%)
	2	94	(28.8%)
	3	10	(3.1%)
Cardiotoxicity	—	9	(2.8%)
Neurotoxicity	—	13	(4.0%)

a lower response and we also noticed a low response in previously transfused patients [20, 21].

The duration of response differed greatly between patients. We had also encouraging results in patients who had received previous chemotherapy or radiotherapy.

Studies on the biochemistry of 5-FU have yielded new information on the mechanism of action and on resistance. We used a bolus injection of folinic acid prior to 5FU 1h infusion, which is in line with preclinical data [10]. Biochemical modulation seems likely to improve the therapeutic efficacy of 5-FU [22, 23]. Prolonged administration of allopurinol can prevent unacceptable toxicity from the combination of folinic acid plus high-dose 5-FU. However, responses with higher doses of 5-FU were not better than those with conventional doses.

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