Anti-Cancer Drugs, 2, pp. 447–451

Treatment of advanced colorectal cancer by 5-fluorouracil–leucovorin combination with or without allopurinol: a prospective randomized study

O Merimsky,[CA] M Inbar and S Chaitchik
The authors are at the Department of Oncology, Ichilov Hospital, Tel-Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 64239, Israel. Fax: 03-5436633.

5-Fluorouracil (5-FU) remains the most effective chemotherapeutic agent in the management of patients with metastatic colorectal cancer. Leucovorin enhances its efficacy, but also its toxicity. Cited data suggest modulation of 5-FU toxicity by high dose allopurinol. In a prospective randomized trial we assessed the ability of allopurinol in a conventional dose to modulate the toxicity of 5-FU–leucovorin combination without compromising its efficacy in 50 patients with advanced colorectal cancer. Twenty-seven patients were randomized for allopurinol but had no benefit in terms of response or reduced toxicity over the other 23. Survival of responders with colon cancer was longer than that of non-responders ($p = 0.013$). Although allopurinol failed to reduce 5-FU–leucovorin toxicity, it did not lower its expected efficacy.

Key words: Allopurinol, colorectal cancer, 5-fluorouracil, leucovorin.

Introduction

Chemotherapy is the mainstay of treatment for patients with metastatic or recurrent colorectal cancer. Studies have demonstrated that biochemical modulation of 5-FU by folinic acid increases its activity against colorectal cancer. 5-FU–leucovorin combination was found to be superior to 5-FU alone in many series.[1,2–12] The exact mechanism by which this combination works synergistically has already been published in detail.[13,14] Dose-limiting toxicity of the combined approach is a major problem, and generally includes mucositis, vomiting, diarrhea, fever, myelosuppression, granulocytopenia, sepsis and death.[3,6,12]

In an attempt to lower the toxicity and to protect the normal cells from undesired effects, allopurinol has been suggested as a protective agent. The biochemical mechanism of its action is reported elsewhere, and is based on competitive inhibition of orotate phosphoribosyltransferase which activates 5-FU intracellularly.[15–20] Systemic administration of high dose allopurinol (600 mg/day) allowed the use of higher doses of 5-FU without increasing the toxicity.[21] However, response rate was significantly compromised by the allopurinol.[21] Patterns of toxicity associated with 5-FU–allopurinol combination were the same as for 5-FU alone, with a predominance of mucositis and mild myelosuppression.[21]

We have conducted a prospective randomized study to assess the ability of a conventional dose of allopurinol (300 mg/day) to modulate the toxicity of 5-FU–leucovorin combination without decreasing its efficacy in patients with advanced or recurrent colorectal cancer.

Patients and methods

Patients

From June 1988 to October 1989, 53 patients were admitted to our Institute of Oncology and found to be suitable for treatment protocol with 5-FU and leucovorin combination. Inclusion criteria were: histologically proven primary disease and measurable recurrent or metastatic disease (clinically, radiologically or by laboratory tests); age between 18 and 85 years; Karnofsky's performance status (KPS) above or equal to 60%; life expectancy of more than 3 months; and ability to be treated

[CA] Corresponding Author

ambulatorily. Patients with any previous treatment were also included. Patients with CNS or spinal cord involvement were excluded.

Treatment protocol

All the patients received the treatment on an out-patient schedule. Baseline evaluation included physical examination, chest X-rays, CT of the abdomen and pelvis, ultrasound of the liver, complete blood count, biochemistry panel and serum CEA. Blood tests, including CEA, were performed before each course of chemotherapy.

Treatment protocol consisted of five consecutive days of leucovorin (200 mg/m^2) drip i.v., followed 1 h later by 5-FU (370 mg/m^2) in a 1-h infusion. Anti-emetic treatment included low dose metoclopramide (30–50 mg) by i.v. drip. Allopurinol (100 mg) was given orally three times daily, starting 24 h prior to the administration of 5-FU–leucovorin, over a period of 7 days.

Evaluation of response and toxicity

Repeated physical examination, abdomino-pelvic ultrasound and CT studies, chest X-rays, biochemical blood analysis and serum CEA determination were used to assess response to treatment. Response and toxicity were graded according to the WHO criteria, as published by Miller *et al.*[22]

Statistical analysis

The chi-squared test was used for statistical analysis. All p values below 0.05 were considered significant.

Results

Patients characteristics

Fifty patients out of 53 who entered the study were evaluated for response and toxicity. Three patients were lost to follow-up after one course of chemotherapy and were not evaluated for either response or toxicity. The age of the 50 evaluable patients ranged from 24 to 82 years, with a median of 65. Twenty-six were males and 24 females. All the patients had histologically proven primary disease and clinically, radiologically and/or biochemically detected and measurable recurrent or metastatic disease. Forty-six patients had KPS equal to or above 80% and four 60–70%.

The primary disease was colon cancer in 32 patients and rectal cancer in 18. Of the 49 patients with histology of adenocarcinoma, 20 had also ulcerated lesions. The 50th patient, the youngest in our series, had a signet ring cell carcinoma. Concomitant benign polyps were found in 11 patients.

The primary pathological staging was Dukes' B_1 in 2 patients, B_2 in 15, C_1 in 7 and D in 26.

Previous treatments included surgery only in 10 patients; surgery with adjuvant radiotherapy in 15 patients; surgery with perioperative adjuvant 5-FU chemotherapy in 4; 5-FU containing chemotherapy for recurrent or metastatic disease in 10; surgery, adjuvant radiotherapy for the primary tumor and chemotherapy for recurrent or metastatic disease in 7 patients. Only 4 patients had no previous treatment. Previous treatments are summarized in Table 1.

Response

The overall response rate (RR) = complete response (CR) + partial response (PR) for patients with colorectal disease was 18% for a median duration of 5 months. There was no complete response. Partial response was observed in five (15.6%) of the patients with colon cancer for a median duration of 5 months, and in four (22.2%) patients with rectal cancer for a median of 6 months. Stable disease was documented in three (16.6%) patients with rectal cancer for 2, 4 and 4 months, respectively, and in one (3%) patient with colon cancer for 8 months. Responses were evaluated separately according to CEA level, site of disease and origin of the primary tumor—colon, or rectum.

Table 1. Previous treatments in colon and rectal cancer patients

Treatment	Rectal cancer	Colon cancer
Surgery only	1	9
Surgery + adjuvant RT	13	2
Surgery + adjuvant perioperative CT	0	4
Surgery + CT for metastatic disease	0	10
Surgery + adjuvant RT + CT for metastatic disease	4	3
No previous treatment	0	4
Total	18	32

RT, radiotherapy; CT, chemotherapy.

CEA levels decreased significantly in both rectal and colon cancer patients. Abdominal spread responded in both groups, while liver and lung metastases responded only minimally in the rectal cancer patients (Table 2).

Median survival of responding patients with colon cancer was significantly longer than median survival for non-responders (13.5 months vs 6 months, $p = 0.013$). Median survival of responders with rectal cancer was insignificantly longer than median survival of progressors (8 months vs 5 months).

We analysed statistically the response in each site of metastasis or in the marker, and compared it to the generally expected response rate of colorectal cancer to 5-FU–leucovorin combination. In patients with rectal cancer, local recurrence responded less than anticipated. The only parameter that showed significantly higher response rate than expected, was the CEA: 77% (stable disease (SD) + minimal response (MR) + PR) for a median duration of 4 months ($p = 0.0022$). In the colon cancer group, liver metastases had a significantly lower response rate (7.4%) than expected ($p = 0.001$). This may be due to previous exposure to 5-FU. The marker responded in 42.8% of cases, but the rate was not significantly higher than that expected.

Toxicity

Toxicity was documented in 50% of the patients. There was one treatment-related death due to leukopenia and septic shock. Another five patients with grade IV toxicity required hospitalization. The others were treated in the out-patient clinic. Side effects are summarized in Table 3.

No correlation was found between response and toxicity in the entire group of colorectal cancer patients (Table 4). However, in the rectal cancer patients, there was a tendency toward improved response in those who experienced toxicity ($p = 0.091$).

Table 2. Response per site of disease. MR and SD were also included provided there was progression of disease prior to the treatment

Primary tumor	Site of disease	Type of response	Frequency	Duration of response (months)
Rectum	Local recurrence	MR	1/12	20
		SD	2/12	4,6
	Liver	SD	2/7	4,14
	Lung	MR	1/2	20
	Marker[a]	PR	3/13	3,4,8
		MR	1/13	2
		SD	6/13	2,2,4,4,20
Colon	Abdominal spread	PR	1/4	3
		SD	1/4	8
	Liver	PR	1/27	12
		SD	1/27	9
	Marker[a]	PR	6/28	2,2,3,5,9,12
		MR	3/28	1,2,2
		SD	3/28	3,3,8

[a] Drop in CEA level was evaluated according to response criteria. But was not considered response.

Allopurinol administration

Twenty-seven patients were randomized to have allopurinol, and 23 placebo. Allopurinol did not reduce the expected toxicity of 5-FU–leucovorin in any of the responders or the non-responders (Table 5), nor did it reduce the expected response rate in our patients to this combination (Table 6).

Discussion

Our group of patients was heterogenous and consisted of pretreated patients in whom 5-

Table 3. Toxicity of 5-FU–leucovorin (WHO criteria)

Side effect	Grade I	Grade II	Grade III	Grade IV
Oral mucositis	2	1	1	5
Nausea, vomiting	6	2	2	4
Diarrhea	8	4	4	5
Cutaneous	1	–	–	–
Decrease in hemoglobin	1	2	1	–
Decrease in WBC count	–	–	3	1
Infection	1	–	2	1
Pain	2	–	2	–

Table 4. The relationship between response, toxicity and allopurinol administration

	Responders	Non-responders
Colon cancer (32 pts)		
Toxicity	+A 0%	+A 25%
	−A 9%	−A 13%
No toxicity	+A 6%	+A 19%
	−A 3%	−A 25%
Rectal cancer (18 pts)		
Toxicity	+A 17%	+A 11%
	−A 11%	−A 11%
No toxicity	+A 0%	+A 22%
	−A 6%	−A 22%

+A, With allopurinol; −A, without allopurinol.

Table 5. Frequency of side effects in 24 patients who experienced toxicity, with or without allopurinol

	Rectum	Colon
With allopurinol	21%	33%
No allopurinol	17%	29%

Table 6. Influence of allopurinol administration on response in patients with colorectal cancer

	Responders	Non-responders
Colon cancer (32 pts)		
With allopurinol	6%	47%
Without allopurinol	12%	35%
Rectal cancer (18 pts)		
With allopurinol	17%	39%
Without allopurinol	22%	22%

FU–leucovorin combination was given as second or third line, as well as patients not previously exposed to 5-FU. The response rate to 5-FU–leucovorin in our trial was in the range of response rates published in the literature: 12–33%.[1,11,12,23] In our study, 67% of the responders had no previous exposure to 5-FU, while 33% had already been treated with 5-FU-containing protocols. Of the non-responders, 44% had experienced 5-FU and 56% had not. Other authors have reported a 0–20% response rate to 5-FU–leucovorin in patients who had previously progressed on 5-FU chemotherapy.[3,12,23] The patients in our series had advanced disease, rendering them responsive at a lower rate and for shorter periods than in other series.

A trend towards improved response was found in rectal cancer patients who experienced toxicity. In this group of patients, the drop in the serum marker level was significantly better than response of the disease in various sites. The reason for this observation is unknown. In colon cancer patients, liver metastases responded at a lower rate than expected, probably due to previous exposure to chemotherapy in a few of them. Median survival of responders was significantly longer than that of non-responders, as also reported by others.[3,10,12] Allopurinol administration did not reduce the expected response rate of colorectal cancer to 5-FU–leucovorin combination, as reported by Howell *et al.*[21] Allopurinol failed to minimize the expected toxicity to this combination in either the responders, or the non-responders. Fox *et al.* reported a response rate of 50% to 5-FU–allopurinol combination.[24] Howell *et al.* could not reproduce this result, receiving no response in 10 patients with colorectal cancer treated with 5-FU and a high dose of allopurinol, but succeeded in significantly lowering toxicity on administration of a high dose of 5-FU.[21]

To conclude, we found moderate activity of 5-FU–leucovorin in patients with advanced colorectal cancer. Allopurinol, given in a conventional dose, failed to reduce the toxicity of this combination.

References

1. Valone FH, Friedman MA, Wittlinger PS, *et al.* Treatment of patients with advanced colorectal carcinomas with fluorouracil alone, high dose leucovorin plus fluorouracil, or sequential methotrexate, fluorouracil and leucovorin: a randomized trial of the Northern Californian Oncology Group. *J Clin Oncol* 1989; **7**: 1427–36.
2. Bacher R, Kurschel E, Kloka O, *et al.* Phase II study with 5FU and leucovorin. *Proc ECCO* 1987; **4** (Abstract 143).
3. Machover D, Schwarzenberg L, Goldschmidt E, *et al.* Treatment of advanced colorectal and gastric adenocarcinomas with 5FU combined with high dose folinic acids: a pilot study. *Cancer Treat Rep* 1982; **65**: 1803–7.
4. Bruckner HW, Ohnuma T, Hart P, *et al.* Leucovorin potentiation of 5-fluorouracil efficacy and potency. *Proc Am Assoc Cancer Res* 1982; **23**: 434.
5. Madajewich S, Petrelli V, Rustum YM, *et al.* Phase I–II trial of high dose calcium leucovorin and 5-fluorouracil in advanced colorectal carcinoma. *Cancer Res* 1984; **44**: 4667–9.
6. Hines JD, Zakem MH, Adelstein DJ, Rustum YM. Treatment of advanced stage colorectal adenocarcinoma with fluorouracil and high dose leucovorin-calcium: a pilot study. *J Clin Oncol* 1988; **6**: 142–6.
7. Petrelli N, Herrera L, Rustum Y, *et al.* A prospective randomized trial of 5-fluorouracil vs. 5-fluorouracil and high dose leucovorin vs. 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987; **5**: 1559–65.
8. Nobile UT, Vidili MG, Sobrero A, *et al.* 5-Fluorouracil alone or in combination with high dose folinic acid in advanced colorectal cancer patients. A randomized trial. *Proc ASCO* 1988; **7**: 97.
9. Doroshow JH, Bertrand M, Multhauf P, *et al.* Prospective randomized trial comparing 5-FU vs. 5-FU and high dose folinic acid for treatment of advanced colorectal cancer. *Proc ASCO* 1987; **6**: 96.
10. Poon MA, O'Connell MJ, Moertel CG, *et al.* Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. *J Clin Oncol* 1989; **7**: 1407–18.
11. Petrelli N, Douglass HO, Herrera L, *et al.* The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. *J Clin Oncol* 1989; **7**: 1419–26.

12. Erlichman C, Fine S, Wong A, Elhakim T. A randomized trial of fluorouracil and folinic acid in patients with metastatic colorectal carcinoma. *J Clin Oncol* 1988; **6**: 469–75.
13. Waxman S, Bruckner H. The enhancement of 5-fluorouracil antimetabolic activity by leucovorin, menadione and α-tocopherol. *Eur J Cancer Clin Oncol* 1982; **18**: 685–92.
14. Evans RM, Laskin JD, Hakala MT. Effects of excess folates and deoxyinosine on the activity and site of action of 5-fluorouracil. *Cancer Res* 1981; **41**: 3283–95.
15. Fox RM, Wood MH, O'Sullivan WJ. Studies on the coordinate activity and liability of orotidylate phosphoribosyltransferase and decarboxylase in human erythrocytes, and the effects of allopurinol administration. *J Clin Invest* 1971; **50**: 1050–60.
16. Bearmore ID, Kelley WN. Effects of allopurinol and oxipurinol on pyrimidine biosynthesis in man. In: Sperling O, DeVries S, Wyngaarden JB, eds. *Purine Metabolism in Man*. New York: Plenum Publishing Corp. 1974: 609–19.
17. Brown GK, O'Sullivan WJ. Inhibition of human erythrocyte orotidylate decarboxylase. *Biochem Pharmacol* 1977; **26**: 1947–50.
18. Fox RM, Royse-Smith D, O'Sullivan WJ. Orotinuria induced by allopurinol. *Science* 1970; **168**: 861–6.
19. Schwartz PM, Handschumacher RE. Selective antagonism of 5-fluorouracil cytotoxicity by 4-hydroxypyrazolopyrimidine (allopurinol) *in vitro*. *Cancer Res* 1979; **39**: 3095–101.
20. Schwartz PM, Dunigan JM, Marsh JC, Handschumacher RE. Allopurinol modification of the toxicity and antitumor activity of 5-fluorouracil. *Cancer Res* 1980; **40**: 1885–9.
21. Howell SB, Wung WE, Taetle R, *et al*. Modulation of 5-fluorouracil toxicity by allopurinol in man. *Cancer* 1981; **48**: 1281–9.
22. Miller A, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1987; **47**: 207–14.
23. Bruckner HW. Comments on the use of leucovorin as a potentiator of 5-fluorouracil. *Cancer Invest* 1988; **6**: 233–4.
24. Fox RM, Woods RL, Tattersall MHN. Allopurinol modulation of high dose fluorouracil toxicity. *Lancet* 1979; **1**: 677.

(Received 22 August 1991; accepted 29 August 1991)