ANTICANCER RESEARCH *17:* 2715-2720 (1997)

Advanced Colorectal Cancer, Refractory to Infusional Fluorouracil Treatment: Efficacy of Second Line Fluorouracil in Combination with a Different Biochemical Modulation

H.K. VAN HALTEREN[1], D.J.Th. WAGENER[2], G. VREUGDENHIL[1] and C.J.A. PUNT[2]

[1]St. Joseph Hospital, Department of Internal Medicine, PO Box 7777, 5500 MB Veldhoven;
[2]University Hospital Nijmegen, Department of Medical Oncology, PO Box 9101, 6500 HB Nijmegen, The Netherlands

Abstract. *Background: Currently there is no standard second line treatment for patients with advanced colorectal cancer (ACC). Previous reports have demonstrated that some patients may benefit from second line infusional 5-fluorouracil (5-FU) after failing 5-FU bolus treatment. Patients and methods: We retrospectively studied the efficacy and toxicity of infusional 5FU regimens given in second line, which only differed from the first line regimen in the type of biochemical modulation and compared these results in a non-randomized fashion to the outcome of patients receiving supportive care only in second line. Results: Sixty six patients with ACC were treated in first line with an infusional 5-FU-based schedule. At the time of disease progression 38 patients received supportive care only. The remaining 28 patients continued treatment with the same 5-FU regimen, but with another biochemical modulator. Fourteen patients achieved stable disease for a median duration of 6 months and one patient achieved a complete remission which lasted 34 months. The median survival from the time of disease progression on first line treatment was 7 months for patients who received second line treatment, whereas those who received supportive care survived for a median period of 3 months ($p<0.05$). Conclusion: Changing the type of biochemical modulation of infusional 5-FU as a second line treatment-alternative may be of some benefit to a subgroup of patients with ACC.*

5-Fluorouracil (5-FU) is the most widely used agent in the treatment of advanced colorectal carcinoma (ACC). During the last decades research has focussed on the optimal administration-schedule of 5-FU and on agents which biochemically modulate the cytotoxic effect of 5-FU. 5-FU may be administered either as bolus or as continuous infusion. While higher response rates generally have been reported for continuous infusion schedules, this has not yet resulted in a survival benefit (1,2). Agents that effectively modulate 5-FU activity are leucovorin (LV) and methotrexate (MTX) (3,4). Other modulators that have been tested in clinical trials include interferon-α (IFN-α) and N-phosphonacetyl-L-aspartic acid (PALA) (5,6). For patients resistant to first line treatment with 5-FU no standard treatment is available. Several small studies have been published on the use of infusional 5-FU in patients resistant to 5-FU bolus therapy (7-10). No data exist on the efficacy of second line treatment with infusional 5-FU in combination with a different biochemical modulator and only very few studies have been reported on second line bolus 5-FU in combination with a different biochemical modulator. The rationale behind these options is that the mechanisms underlying 5-FU resistance might differ depending on the kind of 5-FU schedule or the type of biochemical modulator used. We studied the efficacy and toxicity of infusional 5-FU regimens given in second line, which only differed from the first line regimen in the type of biochemical modulation.

Correspondence to: Dr. C.J.A. Punt, Department of Medical Oncology, University Hospital, PO Box 9101, 6500 HB Nijmegen, The Netherlands.

Key Words: Colorectal carcinoma, neoplasms, second line treatment, 5-fluorouracil, biochemical modulation, 5-fluorouracil resistance.

Patients and Methods

From 1988 until 1993 66 patients with ACC were entered in 3 different studies (11-13). In all patients an infusional 5-FU regimen of 60 mg/kg/48 hours was used. The treatment schedules used in these studies are shown in Table I. Response was evaluated with an interval of 2 to 3 months. Complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD) were defined according to WHO criteria.

Of these 66 patients 28 patients with PD continued treatment with the same schedule of 5-FU, but with a different biochemical modulator than the one used in first line treatment. Patients initially treated with 5-FU alone received 5-FU plus LV and patients initially treated with 5-FU plus LV and IFN-α received 5-FU and MTX. Furthermore, patients treated with 5-FU, PALA and MTX received 5-FU and LV and patients treated with 5-FU and MTX received 5-FU and LV. The major selection criteria for second line chemotherapy were performance status, motivation of the patient for further chemotherapy, as well as adequate liver, bone marrow and renal function.

0250-7005/97 $2.00+.40

Table I. *Schedules according to which the 66 patients studied had been treated.*

Regimen	Drug name	Number of patients	Dose administered	Mode of ad--ministration	Time of ad--ministration
A[11]	5-FU	16	60 mg/kg	continuous iv. over 48 hours	day 1,2
B[11]	5-FU	24	60 mg/kg	continuous iv. over 48 hours	day 1,2
	MTX		40 mg/m^2	bolus iv.	day 1
C[13]	5-FU	4	60 mg/kg	continuous iv. over 48 hours	day 2,3
	MTX		40 mg/m^2	bolus iv.	day 2
	PALA		250 mg/m^2	bolus iv.	day 1
D[12]	5-FU	22	60 mg/kg	continuous iv. over 48 hours	day 1,2
	LV		90 mg	orally	every 6 hours for a total of 8 doses
	IFN-α		10 million units	s.c.	day 1,3 and 5

Treatment was given every week during the first month and every 2 weeks thereafter (c.i.v.=continuous intravenous infusion; i.v.=intravenous; s.c.=subcutaneous; numbers correspond with references).

Patients who did and patients who did not receive second line chemotherapy were compared in terms of overall survival, response rate to first line chemotherapy and progression-free survival, as well as performance status at the time of discontinuation of first line chemotherapy. Furthermore, we analyzed whether second line chemotherapy contributed to a longer survival. For this part of the analysis survival was measured from the moment of disease progression during first line chemotherapy. The significance of differences between stochastic variables was estimated by means of the Chi-square test. The significance of differences between actuarial survival curves was estimated by means of the Anderson log rank-test.

Results

For the entire group of 66 patients first line chemotherapy resulted in 34 SD's (52%) and 8 PR's (12%). CR's did not occur. In 24 cases (36%) the disease appeared progressive. The median progression-free interval was 6 months.

After disease progression twenty eight patients continued chemotherapy with the same 5-FU schedule, but with a different biochemical modulator. Table II shows the responses and survival of these patients. Fourteen patients (50%) achieved SD for a median duration of 6 months and one patient (4%) achieved a CR which lasted 34 months. The median progression-free interval was 4 months. Median survival measured from the moment of disease progression during first line treatment was significantly better for the 28 patients who had received second line chemotherapy than for the 38 patients who had received supportive care only (7 months *versus* 3 months, $p<0.05$).

Grade I-II toxicities occurred in 17 patients on second line chemotherapy (61 %) and grade III gastrointestinal toxicity occurred in one patient (4%).

As shown in Tables III and IV, the patients who received second line chemotherapy differed considerably from the patients who received supportive care only. Among former the proportion of patients with SD or a PR to first line chemotherapy was higher ($p<0.05$) and the median

Table II. *Characteristics of the patients who underwent second line treatment.*

Patient No.	Gender	Age (yrs.)	First line therapy			Second line therapy			Overall survival (months)
			schedule	response	response duration (months)	schedule	response	response duration (months)	
1	M	44	5-FU	SD	13	5-FU/LV	CR	34	53
2	F	51	5-FU	PD	*	5-FU/LV	PD	*	24
3	M	53	5-FU	PD	*	5-FU/LV	PD	*	8
4	M	64	5-FU	SD	4	5-FU/LV	SD	6	12
5	M	45	5-FU	SD	9	5-FU/LV	SD	4	13
6	M	47	5-FU/LV/IFN	SD	10	5-FU/MTX	PD	*	22
7	M	50	5-FU/LV/IFN	PR	14	5-FU/MTX	SD	19	51
8	M	46	5-FU/LV/IFN	SD	16	5-FU/MTX	SD	6	30
9	M	54	5-FU/LV/IFN	SD	20	5-FU/MTX	SD	6	30
10	M	43	5-FU/LV/IFN	PR	10	5-FU/MTX	PD	*	24
11	M	59	5-FU/LV/IFN	PR	9	5-FU/MTX	SD	5	26
12	M	41	5-FU/LV/IFN	PR	18	5-FU/MTX	SD	5	25
13	M	66	5-FU/MTX PALA	PR	15	5-FU/LV	SD	6	32
14	M	68	5-FU/MTX PALA	PD	*	5-FU/LV	PD	*	12
15	M	67	5-FU/MTX	SD	15	5-FU/LV	SD	6	23
16	F	51	5-FU/MTX	SD	6	5-FU/LV	PD	*	15
17	M	59	5-FU/MTX	SD	9	5-FU/LV	SD	4	13
18	M	46	5-FU/MTX	SD	6	5-FU/LV	PD	*	8
19	M	57	5-FU/MTX	SD	6	5-FU/LV	SD	13	19
20	M	56	5-FU/MTX	SD	9	5-FU/LV	SD	5	15
21	M	44	5-FU/MTX	PD	*	5-FU/LV	PD	*	7
22	M	29	5-FU/MTX	PR	9	5-FU/LV	PD	*	15
23	M	52	5-FU/MTX	SD	6	5-FU/LV	PD	*	14
24	M	50	5-FU/MTX	SD	19	5-FU/LV	SD	5	44
25	M	52	5-FU/MTX	SD	9	5-FU/LV	PD	*	22
26	F	66	5-FU/MTX	PD	*	5-FU/LV	PD	*	7
27	F	56	5-FU/MTX	PD	*	5-FU/LV	SD	6	12
28	M	60	5-FU/MTX	SD	17	5-FU/LV	PD	*	21

An overview of all patients who received first and second line treatment for advanced colorectal cancer (CR, PR, SD and PD denote complete response, partial response, stable disease and progressive disease, respectively; M=male; F=female;
1=calculated from the start of first line therapy .

Table III. *Survival percentages according to type of treatment.*

Duration of follow up	Entire group (n=66)	Patients who received second line chemotherapy (n= 28)	Patients who did not receive second line chemotherapy (n= 38)
6 months	76%	100%	64%
12 months	45%	75%	28%
18 months	28%	54%	8%
24 months	16%	29%	5%

Actuarial overall survival of 66 patients with advanced colorectal cancer who received chemotherapy and survival of the subgroups who did (n= 28) and who did not (n= 38) receive second line chemotherapy.

Table IV. *Baseline characteristics of the two treatment groups.*

	Second line chemotherapy (n= 28)	No second line chemotherapy (n=38)
Gender		
male	n= 23 (82%)	n= 28 (74%)
female	n= 5 (18%)	n= 10 (26%)
Median age	52 years	52 years
Site of metastases		
liver with or without lungs	n= 22 (79%)	n= 25 (66%)
lungs	n= 1 (3%)	n= 8 (21%)
locoregional	n= 3 (11%)	n= 2 (5%)
other	n= 2 (7%)	n= 3 (8%)
Response to first line chemotherapy		
PD	n= 6 (21%)	n= 18 (47%)
SD/PD	n= 21 (79%)	n= 20 (53%)
Percentage of patients free from progression after first line chemotherapy		
6 months follow up	65%	28%
12 months follow up	33%	8%
18 months follow up	7%	0%
Median Karnofsky performance status at the time of discontinuation of first line treatment	90%	70%

Characteristics of patients with advanced colorectal cancer who did and who did not receive second line chemotherapy (PD=progressive disease), SD=stable disease, PR=particle remission.

progression-free interval from the start of first line chemotherapy was longer (8 months *vs* 3 months, $p < 0.01$). Their median Karnofsky performance status was better at the time of discontinuation of first line chemotherapy (90% *vs* 70%). Furthermore, their median overall survival from the start of first line treatment was significantly longer (20 *vs* 8 months, $p< 0.001$).

Discussion

At present, most patients with ACC are treated in first line with a 5-FU-based regimen. In case of progression, there is no standard second line regimen available. Several studies indicate that in some patients with disease progression on first line treatment with bolus 5-FU a response or stabilization of disease can be induced by administration of an infusional schedule with high-dose 5-FU (7-10). In these studies response rates (CR and PR) varied from 5% to 30% with a median overall survival of 7.5 months to 10 months.

Our study adresses the question whether patients with ACC refractory to treatment with a combination of infusional 5-FU and one or more biochemical modulators may benefit from a second line regimen consisting of the same 5-FU schedule, but with a different modulator. Publications concerning this question are scarce. Bernhard *et al* (14) studied the value of the addition of IFN-α in 15 patients refractory to treatment with 5-FU and LV. Only one minor response and one SD were observed; In a study performed by Palmieri *et al* (15) 20 patients with ACC refractory to treatment with 5-FU or 5-FU plus LV received a second line schedule consisting of 5-FU and MTX. Two PR's were observed and 12 patients achieved SD. The second line schedules used in our study (infusional 5FU plus MTX or LV) resulted in 50% SD and one CR in 28 patients.

In our study, the baseline characteristics of the patients who received second line chemotherapy clearly differed from those of patients who received supportive care only. A larger proportion had benefitted from first line chemotherapy in terms of response and response duration. Furthermore, they were in better condition at the time of disease progression on first line treatment. Second-line treatment was not initiated in a prospective randomized fashion and therefore the patients that received second line treatment represent a selected group of patients. Because the patients receiving second line treatment comprised a group with a better prognosis compared to the group receiving supportive care only, a direct comparison between the two groups cannot be made and the difference in overall survival may not be attributed directly to the second line treatment. However, our results suggest that selected patients refractory to infusional 5-FU may have some benefit from second line treatment with infusional 5-FU in combination with a different biochemical modulator. Alternative possibilities for the treatment of 5-FU resistant colorectal cancer are irinotecan (CPT-11) (16) and 5-FU-modulation by trimetrexate (17), since these agents have shown promising results in phase II studies.

References

1 Lokich JJ, Ahlgren JD, Gullo, Philips JA, Fryer JG: A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a mid-atlantic oncology program study. J Clin Oncol *7:* 425-432, 1989.

2 Weinerman B, Shah A, Fields A, *et al:* Systemic infusion versus bolus chemotherapy with 5-fluorouracil in measurable metastatic colorectal cancer. Am J Clin Oncol *15:* 518-523, 1992.

3 Advanced Colorectal Cancer Meta-analysis project. Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. J Clin Oncol *10:* 896-903, 1992.

4 Advanced Colorectal Cancer Meta-analysis Project. Meta-analysis of randomized trials testing the biochemical modulation of fluorouracil by methotrexate in metastatic colorectal cancer. J Clin Oncol *12:* 960-969, 1994.

5 Wadler S, Schwartz EL, Goldman M: Fluorouracil and recombinant alfa-2a interferon: an active regimen against advanced colorectal carcinoma. J Clin Oncol *7:* 1769-1775, 1989.

6 Ardalan B, Singh G, Silberman H: A randomized Phase I and II study of short term infusion of high-dose fluorouracil with or without N-(phosphonacetyl)-L aspartic acid in patients with advanced pancreatic and colorectal cancers. J Clin Oncol *6:* 1053-1058, 1988.

7 Ardalan B, Chua L, Tian E *et al:* A phase II study of weekly 24 hour infusion with high dose fluorouracil and leucovorin in colorectal carcinoma J Clin Oncol *9:* 625-630, 1991.

8 Weh HJ, Wilke HJ, Dierlamm J, *et al:* Weekly therapy with folinic acid (FA) and high dose 5-fluorouracil (5-FU) 24-hour infusion in pretreated patients with metastatic colorectal carcinoma. Ann Oncol *5:* 233-237, 1994.

9 Mori A, Bertoglio S, Aschele C: Activity of continuous infusion 5-fluorouracil in patients with advanced colorectal cancer clinically resistant to bolus 5-fluorouracil. Cancer Chemother Pharmacol *33:* 179-180, 1993.

10 Falcone A, Cianci C, Pfanner E, *et al:* Continuous infusion 5-fluorouracil in metastatic colorectal cancer patients pretreated with bolus 5-fluorouracil: clinical evidence of incomplete cross-resistance. Ann Oncol *5:* 291, 1994.

11 Blijham G, Wagener T, Wils J *et al:* Modulation of high-dose infusional fluorouracil by low-dose methotrexate in patients with advanced or metastatic colorectal cancer: final results of a randomized European Organization for Research and Treatment of Cancer study. J Clin Oncol *14:* 2266-2273, 1996.

12 Punt CJA, Burghouts JThM, Croles JJ, *et al:* Continuous infusion of high-dose 5FU in combination with leucovorin and recombinant interferon-alpha-2b in patients with advanced colorectal cancer. Cancer *72:* 2107-2111, 1993.

13 EORTC 4090-study: The modulation of high-dose 5-FU with low-dose methotrexate and N-phosphonacetyl-L-aspartic acid (PALA) in patients with advanced colorectal cancer; unpublished data.

14 Bernhard H, Klein O, Meyer zum Buschenfelde KH, Knuth A: Treatment of refractory colorectal carcinomas with fluorouracil, folinic acid and interferon alfa-2a. Semin Oncol *19*(2 suppl 3): 204-207, 1992.

15 Palmieri G, Gridelli C, Airoma G, *et al:* Second-line chemotherapy of advanced colorectal cancer with sequential high-dose methotrexate and 5-fluorouracil. J Chemother *3:* 55-60, 1991.

16 Shimada Y, Yoshino M, Wakui A. Phase II study of CPT-11, a new camptothecin derivative, in metastatic colorectal cancer. J Clin Oncol *11:* 909-913, 1993.

17 Conti JA, Kemeny N, Seiter K, *et al:* Trial of sequential trimetrexate, fluorouracil and high-dose leucovorin in previously treated patients with gastrointestinal carcinoma. J Clin Oncol *12:* 695-700, 1994.

Received February 2, 1997
Accepted March 14, 1997