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CLINICAL TRIAL REPORT

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5-Fluorouracil and low-dose leucovorin in metastatic colorectal cancer: a pilot study

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Abstract A total of 56 consecutive patients with metastatic colorectal cancer received treatment with 5-fluorouracil (5-FU) given at 425 mg/m^2 by rapid intravenous infusion, immediately preceded by leucovorin (LV) given at 20 mg/m^2, with cycles being repeated every 4 weeks. Of 48 evaluable patients undergoing this treatment, a tumor response was observed in 16 (33%); a complete response, in 2 (4%); and a partial response, in 14 (29%). The median survival was 8.5 months for all patients and 16.5 months for responders. An improvement in symptoms was seen in 9 (26%) of 34 symptomatic patients. In all 15 (27%) of 44 evaluable patients showed an improvement in performance status. The most significant toxicity attributable to the treatment was mucositis of grade 3 or 4, seen in 27% of the patients. Altogether, 2 patients (3.5%) were hospitalized for treatment-related toxicity. We conclude that the combination of 5-FU and low-dose LV is active in advanced colorectal cancer and is associated with acceptable toxicity.

Key words Colorectal cancer · 5-Fluorouracil · Low-dose leucovorin

Introduction

The cytotoxic activity of 5-Fluorouracil (5-FU) can be potentiated by leucovorin (LV) [8,19]. Several studies have shown that the combination of 5-FU and LV in the treatment of advanced colorectal cancer is advantageous in terms of tumor response as compared with that due to 5-FU alone [1]. However, the optimal schedules of this combination have not been determined. In one randomized trial, Petrelli et al. [14,15] compared three treatment regimens: (1) high-dose LV (500 mg/m^2) + 5-FU (600 mg/m^2) given on day 1 and weekly thereafter, (2) low-dose LV (25 mg/m^2) + 5-FU (600 mg/m^2) given on day 1 and weekly thereafter, and (3) escalated LV dosing (25 to 250 to 500 mg/m^2) together with 5-FU (1,000 mg/m^2) given on day 1 and every 21 days afterward. This team found that the higher LV doses were associated with better response rates.

However, Poon et al. [16,17] differed from this conclusion in comparing (1) LV (20 mg/m^2) + 5-FU (425 mg/m^2) given for 5 days every 4–5 weeks, (2) LV (200 mg/m^2) + 5-FU (370 mg/m^2) given for 5 days every 4–5 weeks, and (3) 5-FU + high-dose methotrexate with LV rescue. They found, by contrast, that the low-dose LV regimen was associated with better survival after covariate analysis. At the Northern Israel Oncology Center, we have been using low-dose LV with 5-FU for metastatic colorectal cancer, and we report our results in this paper.

Patients and methods

The eligibility criteria for treatment of colorectal cancer patients with this regimen included: (a) pathologically confirmed recurrent or metastatic colorectal adenocarcinoma, (b) no prior chemotherapy, (c) a WHO performance status of 0–3, (d) a serum bilirubin level of < 7 mg/dl, (e) a serum transaminase level of $< 4 \times$ normal, and (f) a serum creatinine value of < 1.5 mg/dl.

The treatment protocol consisted of 5 days of intravenous LV (20 mg/m^2) immediately followed by rapidly infused 5-FU (425 mg/m^2); the cycle was repeated every 4 weeks as long as the WBC was $> 4{,}000$/ml^3, the thrombocyte count was $> 100{,}000$/ml^3, and side effects such as mucositis and diarrhea had resolved. Dose modifications were made during treatment only for 5-FU. There was a 10% reduction in subsequent cycles if any of the following

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Table 1 Characteristics of 56 patients with colorectal cancer

Descriptive parameter	Number (%)	Range (median)
Age (years)		29–86 (61)
Sex (M:F)	27:29	
Performance status (WHO scale):		
0	6 (12%)	
1	29 (58%)	
2	9 (18%)	
3	5 (12%)	
Site of primary tumor:		
Rectosigmoid	26 (46 %)	
Colon	28 (50%)	
Multiple (> 2)	2 (4%)	
Sites of disease:		
Liver	40 (71%)	
Abdominal cavity	22 (40%)	
Lung	13 (25%)	
Primary site and/or Local recurrence	29 (57%)	
Other	5 (10%)	
Prior therapy:		
Surgery for primary tumor	42 (75%)	
Adjuvant radiotherapy	9 (16%)	
Measurable disease:		
Physical examination	21 (39%)	
CT scan	35 (76%)	
Ultrasound	13 (33%)	
Liver scan	12 (21%)	
Chest X-ray	10 (18%)	

developed: grade 3 mucositis, diarrhea, leukopenia, or thrombocytopenia. A 10% increase in the 5-FU dose was carried out in patients with only grade 1 toxicities, if any.

Toxicities and responses were evaluated according to WHO criteria [12]. Patients were evaluated before each course of chemotherapy for the following symptoms, attributable to malignant disease: weakness, loss of appetite, emesis, and abdominal pain. The duration of response and survival were measured from the initiation of chemotherapy. The actual dose intensity was calculated according to the method of Hryniuk and Bush [10].

Results

Between February 1990 and July 1992, 56 consecutive patients were entered in the treatment protocol for advanced colorectal cancer. The characteristics of these patients appear in Table 1. More than half of these patients (57%) had disease at the primary site or a local recurrence; the most common metastatic site was the liver (71%). In all, 8 patients were nonevaluable (5 were absolutely nonevaluable and 3 were evaluable but not completed worked up); the remaining 48 had measurable disease.

An objective response was noted in 16 of 48 evaluable patients (33%; 95% confidence interval, 0.21–0.49), most commonly in the liver (13 patients), lung (2 patients), and abdominal locations other than the liver (2 patients). This included a complete response (CR) in 2 patients (4%) and a partial response (PR) in 14 (29%). The 2 patients who achieved a CR had liver metastates; the CR was documented by normalization of the liver scan in one and by abdominal ultrasonography, liver-function tests, and serum carcinoembryonic antigen (CEA) evaluation in the other. The duration of response ranged from 3 to 19 months (median, 9 months). The median survival for all patients was 8.5 months (range, 2–28 months) and that for responders (complete and partial) was 16.5 months (range, 5–26 months). Nonresponsders survived for 2–28 months (median, 7 months). An improvement in symptoms was seen in 9 of 34 symptomatic patients (26%). The performance status was evaluated during therapy for 44 of 50 patients who had a pretreatment status of ≥ 1; there was an improvement in 15 of the 44 patients (34%).

Table 2 Toxicity encountered during treatment in 56 patients with colorectal cancer

Toxicity parameter	All courses Range (median)	Number of patients
Leukocyte nadir (/ml^3)	1,900–18,000 (4,600)	
Thrombocyte nadir ($\times 10^3$/cm^3)	57–339 (142)	
Hemoglobin nadir (g/dl)	7.8–13.2 (11.0)	
Mucositis:		
Grade 1		6 (11%)
Grade 2		18 (33%)
Grade 3		13 (23%)
Grade 4		2 (4%)
Diarrhea:		
Grade 1		7 (13%)
Grade 2		28 (51%)
Grade 3		5 (9%)
Grade 4		1 (2%)

An evaluation of side effects was done for all patients and appears in Table 2. Myelotoxicity was mild to moderate, and there was only one episode of neutropenic fever. Mucositis was the most significant toxicity encountered (27% of all patients developed grade 3 or 4 mucositis). Grade 3 or 4 diarrhea occurred in 11% of the patients. Hospitalization for toxic side effects was required for 2 (3.5%) patients. Both had grade 3 mucositis (stomatitis) and 1 also had leukopenic fever. The median dose intensity as determined after the initial three cycles was similar in responders and nonresponders (100% versus 95%).

Discussion

The superiority of the 5-FU and LV combination over 5-FU alone in the treatment of advanced colorectal

cancer, as measured by the objective response rate and palliative effect, has been confirmed by ten randomized studies (5–7,9,11,13–19]. These data were recently published in the form of a meta-analysis [1].

The optimal schedule of this combination has yet to be determined. Most of the above-mentioned trials used LV in a daily dose of either 200 or 500 mg/m^2. In two studies published by Petrelli et al. [14,15] and Poon et al. [16,17], low-dose LV with 5-FU was given. Using a weekly schedule, Petrelli et al. [14,15] compared low-dose LV (25 mg/m^2) with high-dose LV (500 mg/m^2), both being given with 5-FU (600 mg/m^2), and found the higher dose to be superior in terms of tumor response (28% versus 19%). Poon et al. [16] compared one treatment arm utilizing 5-FU (370 mg/m^2) plus high-dose LV (200 mg/m^2) with low-dose LV (20 mg/m^2) and 5-FU (425 mg/m^2) given daily for 5 days every 4 weeks and with 5-FU given alone. In this study, no significant difference between the two 5-FU and LV regimens was found; however, in patients with nonmeasurable disease, both were associated with better overall survival than was obtained with 5-FU alone. In the updated study of Poon et al. [17], no significant survival difference between the two 5-FU + LV regimens was found, but after covariate adjustment, the 5-FU + lower-dose LV arm was indeed associated with better survival in patients with measurable and nonmeasurable disease.

A recently published randomized trial [4] of 362 patients receiving 5-FU and LV, either high-dose (the Roswell Park protocol of 500 mg/m^2 LV) or low-dose (20 mg/m^2 LV) regimens showed similar therapeutic effectiveness, but the low-dose regimen emerged as being less toxic and less expensive. A nonrandomized study of 44 patients who received 5-FU (370–375 mg/m^2) with low-dose LV (20 mg/m^2) on days 1–5 every 4–5 weeks, showing a response rate of 17%, concluded that LV contributed only to greater toxicity and not to better response as compared with 5-FU alone [2].

Our study, with an objective response rate of 33% (95% confidence limits, 0.21–0.49) and 2 cases of CR (4%), gives some support to the findings of Poon et al. The toxicity encountered among our patients was acceptable, with no treatment-related mortality; however, 2 patients (3.5%) needed hospitalization for side effects. The most predominant adverse reaction was mucositis (grades 3–4 in 22% of patients) and diarrhea (grades 3–4 in 11%). This finding is also comparable with the toxicity observed by Poon et al. A difference in treatment-related toxicity between weekly and monthly schedules of 5-FU and LV was noted. The dose-limiting toxicity in the former was diarrhea, and that in the latter, as in our study, was mucositis [13]. As might be expected, an improvement in median survival for both responders and non-responders to treatment was seen in our study (16.5 versus 7 months, $P < 0.001$).

As are other authors [3], we are surprised by the dearth of studies reported in the literature on the effectiveness of 5-FU and low-dose LV in advanced colorectal cancer, especially in an era of compelling cost considerations. We conclude that the combination of 5-FU and low-dose LV is a relatively effective treatment for advanced colorectal cancer and causes acceptable toxicity. Our data support the importance of further investigations that would help to throw light on this matter.

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