Prospective Randomized Trial of 5-Fluorouracil *versus* 5-Fluorouracil plus Levamisole in the Treatment of Metastatic Colorectal Cancer: A Hoosier Oncology Group Trial[1]

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ABSTRACT

The purpose of this study was to compare the objective response rate, duration of remission, and survival of 5-fluorouracil (5-FU) *versus* those of 5-FU plus levamisole in metastatic colorectal cancer using the same dose and schedule of these agents as in the North Central Cancer Treatment Group and intergroup studies of adjuvant therapy. Patients with no prior history of chemotherapy for metastatic disease were entered on this Hoosier Oncology Group randomized Phase III trial. Patients were stratified by Karnofsky performance status and presence or absence of liver metastases. They were randomized to receive 450 mg/m^2 5-FU i.v. for 5 days followed by 15 mg/kg i.v. weekly (arm 1) or the same dose of 5-FU plus levamisole 50 mg p.o. every 8 h for 3 days every 2 weeks (arm 2). The duration of treatment for both arms was 26 weeks. From April 1990 to March 1995, 199 patients were entered. One hundred eighty-two patients, 91 in each arm, were fully evaluable. The response rates were 12% on arm 1 and 13% on arm 2. The median duration of response was 18 weeks on both arms. The median survival was 48 weeks on arm 1 and 41 weeks on arm 2 ($P = 0.20$). This study failed to show any improvement in survival, response, or duration of remission with the addition of levamisole to 5-FU in the treatment of metastatic colorectal cancer.

INTRODUCTION

Colorectal carcinoma is the second leading cause of cancer death in the United States. In 1996, it was estimated that 131,200 new cases of colorectal cancer would be diagnosed and that 54,900 men and women would die from this disease (1).

Heidelberger and colleagues (2) at the University of Wisconsin first reported clinical trials with 5-FU[3] in 1957. Since then, 5-FU has been the mainstay of therapy for metastatic colorectal cancer. However, the results with single agent 5-FU reveal only a 10–20% objective response rate, with no impact on survival. Attempts to improve upon this have lead to development of various regimens using biochemical modulation of 5-FU, based upon laboratory and preclinical data. The most popular of these has been the combination of 5-FU and leucovorin, based upon a sound preclinical pharmacological rationale.

There have been various schedules of 5-FU in combination with leucovorin that have demonstrated encouraging results in Phase II trials (3). Subsequently, these have led to Phase III studies in metastatic colorectal cancer evaluating 5-FU (as the control arm) compared to 5-FU plus leucovorin. There has been a lack of congruence in the results from these disparate Phase III studies (4). Review of the 12 published randomized studies comparing 5-FU with 5-FU plus leucovorin reveals that the consistently higher response rate of the combination regimen has failed to translate into significant survival advantage (5–16). These studies all used 5-FU given by i.v. push. Only three studies have shown marginal survival advantage for the combination over 5-FU alone (11, 13, 15). In fact, in one study, the benefit was significant only for patients with nonmeasurable and, hence, probably low volume disease (11). Even a meta-analysis failed to show any significant improvement in survival with 5-FU plus leucovorin (17). Furthermore, combining 5-FU with other agents, such as cisplatin, methotrexate, PALA, and thymidine, has not improved the survival statistics in metastatic colorectal cancer (18–20).

Levamisole is a pure chemical that was first used as an antihelminthic drug and has documented immunomodulatory effects. Verhaegen *et al.* (21) initially evaluated levamisole *versus* placebo in a very small patient population in surgically resected colon cancer and demonstrated a statistically significant survival advantage. The Western Cancer Study Group and the European Organization for Research and Treatment of Cancer compared levamisole to placebo in the adjuvant setting and found no significant survival benefit (22, 23).

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[3] The abbreviations used are: 5-FU, 5-fluorouracil; NCCTG, North Central Cancer Treatment Group; KPS, Karnofsky performance status.

The major interest in levamisole as adjuvant therapy of Duke's B and C colon cancer is because of a positive NCCTG study (24) and a larger confirmatory intergroup study (25), both demonstrating a significant advantage for 5-FU plus levamisole over levamisole alone. However, this dose and schedule of 5-FU plus levamisole has never been adequately tested in metastatic disease. Surprisingly, there have been only three published Phase III studies of 5-FU plus levamisole in metastatic colorectal cancer. Borden *et al.* (26) at the University of Wisconsin published a positive study demonstrating a survival advantage for 5-FU plus levamisole, whereas the NCCTG study was negative (20). However, neither of these studies these used the same dosage and schedule as in the successful adjuvant trials. The study by the Eastern Cooperative Oncology Group, published only in abstract form thus far, was also negative (27). The dose and schedule of 5-FU and levamisole in this trial were also different from those used in the adjuvant studies.

There are few, if any, examples in oncology in which a regimen that provides a significant survival advantage in the adjuvant setting is not also effective in metastatic disease. Therefore, the Hoosier Oncology Group embarked upon this study evaluating 5-FU plus levamisole in previously untreated patients with metastatic colorectal cancer, using dosage and schedule of these agents that were identical to those in the adjuvant trials.

PATIENTS AND METHODS

All patients had histologically proven adenocarcinoma of the colon or rectum and had not received prior chemotherapy for metastatic disease. Patients may have had adjuvant therapy but not within the 6 months prior to registration. Patients with measurable as well as nonmeasurable disease were included. Measurable disease was defined as being bidimensionally measurable on physical or roentgenographic examination. Malignant hepatomegaly could be used as measurable disease if the liver edge was palpable at least 5 cm below the costal margin at the right midclavicular line or xiphoid on quiet respiration. The liver span should have been greater than 12 cm. All patients had a KPS of at least 50%, as well as adequate bone marrow reserve (absolute granulocyte count of 2,500 cells/mm^3 and platelet count of 125,000/μl). Patients were excluded if they had a history of prior malignancy, except squamous or basal cell carcinoma of the skin or carcinoma *in situ* of the cervix, unless they had been disease-free for at least 5 years.

Pretreatment studies included complete history and physical examination, complete blood count including WBC differential and platelet counts, 12-channel sequential multiple analysis, carcinoembryonic antigen measurement, chest X-ray, and abdominal computerized tomographic scan. During treatment, patients were evaluated by history and physical examination every 4 weeks, and radiographs were repeated every 8 weeks for tumor measurement. In addition, a complete blood count including WBC differential and platelet count was obtained every week.

All patients provided written informed consent. Eligible patients were stratified by KPS (80–100 *versus* 50–70) and presence or absence of liver metastases. Patients were then randomized by telephone through the Hoosier Oncology Group office to receive 5-FU alone or 5-FU plus levamisole.

5-FU was administered at a dose of 450 mg/m^2 by i.v. push on days 1–5; thereafter, beginning on day 29, it was given weekly at 15 mg/kg by i.v. push. This was identical for both arms. Patients randomized to the combination arm received 50 mg of levamisole p.o., every 8 h for 3 days, every 2 weeks. The total duration of therapy was 26 weeks. There was no dose escalation of 5-FU, and cross-over to 5-FU plus levamisole was not allowed.

All patients with prior pelvic irradiation received a 25% reduction in the 5-FU dose initially. 5-FU was given as scheduled if the WBC count was greater than 3000 cells/mm^3, and platelet count was greater than 90,000/μl. If counts were below these levels, treatment was held until these levels were reached, and then it was initiated with 25% reduction in the 5-FU dose. If 5-FU was delayed, levamisole was concomitantly delayed, but its dose was not reduced. In cases of severe diarrhea or stomatitis lasting more than 3 days, granulocytopenic fever, or thrombocytopenia requiring platelet transfusion, the dose of 5-FU was reduced by 25% with no change in the levamisole dose.

A complete response was defined as complete disappearance of all objective evidence of disease. A partial response was defined as a decrease of 50% or more in the sum of products of diameters of measurable disease. When malignant hepatomegaly was used for tumor measurement, at least a 30% decrease in the sum of the measurements of the liver edge below the costal margin at the right midclavicular line and the xiphoid process was required for a PR. A decrease of less than 50% in the sum of product of diameters of measurable disease was considered stable disease provided no new lesions had appeared, and an increase of 25% or more or appearance of new lesions defined progression.

Survival was measured from the date entered on study until death. Remission duration was measured from the date of documented response until relapse. Patients who relapsed were treated at the investigator's discretion.

Statistical Considerations. Descriptive statistics are reported as frequencies, medians, and ranges. Grade 3/4 toxicities were compared between the two arms (5-FU *versus* 5-FU + levamisole) using Fisher's exact test (28). Survival was defined from date on study until date of death or date last known alive. Follow-up was the survival of all patients alive. The survival curve for each treatment arm was constructed using the Kaplan-Meier product limit method (29).

Survival curves between the two treatment arms were compared with the log-rank test of survival (30). The association of treatment arm and survival, adjusting for the stratification factors, liver metastases and KPS, was assessed by the Wald χ^2 of Cox's proportional hazards regression (31). All tests were two-sided. The intention-to-treat principle was used throughout.

RESULTS

From April 1990 through March 1995, 199 patients with metastatic adenocarcinoma of the colon or rectum were entered on this trial. Of the 99 patients randomized to 5-FU, 4 patients never received treatment, 1 was lost to follow-up, and 3 had

Table 1 Patient characteristics

	5-FU	5-FU + levamisole
No. of patients registered	99	100
Sex (male/female)	62/37	53/47
Median age (yr)	66	65
Range (yr)	20–86	27–87
KPS		
50–70	24	25
80–100	75	75
Prior pelvic RT[a]	10	11
Metastatic sites		
Liver	79	80
Lung	28	22
Other	22	25

[a] RT, radiotherapy.

Table 2 Treatment compliance

	5-FU (n = 94)	5-FU + levamisole (n = 96)
Completed treatment	32	27
Reasons for discontinuation		
PD[a]	45	48
PSR	4	1
Toxicity	7	12
Noncompliance	4	5
Death[b]	2	4

[a] PD, progressive disease; PSR, poor subjective response (≥20% fall in KPS, 10% weight loss, and increased pain without radiographic documentation of progression).
[b] Not related to disease or therapy.

Table 3 Toxicity (grade 3/4)

	Percentage of patients	
	5-FU	5-FU + levamisole
Anemia	4	1
Granulocytopenia[a]	13	24
Thrombocytopenia	0	2
Nausea	5	5
Vomiting	6	3
Diarrhea[b]	8	21
Stomatitis	5	7
Infection	2	5
Fever	2	1
Neurological	1	6
Death[c]	0	4

[a] P = 0.067.
[b] P = 0.0146.
[c] P = treatment-related only.

inadequate response data. One hundred patients were randomized to 5-FU plus levamisole, of whom 4 never received treatment and 5 had inadequate response data. In all, 182 patients were fully evaluable for survival and response, and another 8 patients were evaluable for survival only.

Patient characteristics are shown in Table 1. Patients on the two arms were well matched for age, KPS, presence or absence of liver metastases, and prior pelvic radiotherapy.

Thirty-two patients on the 5-FU arm and 27 on the 5-FU plus levamisole arm completed 26 weeks of treatment. Reasons for discontinuation of therapy are listed in Table 2. The most frequent reason for early termination of chemotherapy was secondary to tumor progression during therapy.

Toxicity. The toxicity data are shown in Table 3. This table reflects the worst grade of toxicity experienced by each patient at any time while in the study. The higher incidence of grade 3/4 diarrhea in the 5-FU plus levamisole arm was statistically significant (P = 0.0146), whereas the difference in the incidence of grade 3/4 granulocytopenia between the two arms did not reach statistical significance (P = 0.067). There were no treatment-related deaths on the 5-FU arm, whereas there were four on the combination arm.

Response and Survival. There were 23 objective responses in 182 fully evaluable patients. There was one complete response on each arm. Overall, the response rate was 12% (95% CI = 6–21%) on the 5-FU arm and 13% (95% CI = 7–22%) on the 5-FU plus levamisole arm. The median duration of response on both arms was 18 weeks. Thirty-eight patients on the 5-FU arm and 25 patients on the combination arm had stable disease. The median time to progression was 18 weeks on the 5-FU arm and 13 weeks on the 5-FU plus levamisole arm (P = 0.06).

Median survival was 48 weeks on the 5-FU arm and 41 weeks on the 5-FU plus levamisole arm (Fig. 1). Survival times on the two arms were not significantly different by the log-rank test (P = 0.20). In the Cox proportional hazards regression, the Wald χ^2 was 1.968 (P = 0.16; 1 degree of freedom) for treatment arm, adjusting for the stratification factors, liver metastases and KPS. At the time of analysis of this data, 11 patients on the 5-FU arm and 3 on the combination arm were alive.

DISCUSSION

One of the basic principles of medical oncology is that the use of a regimen to improve the surgical cure rate in a malignancy is preceded by documented efficacy in advanced disease. However, the choice of 5-FU plus levamisole in the adjuvant NCCTG trial was quite empirical (24). This dose and schedule of these agents had never been adequately tested in metastatic colorectal cancer.

The University of Wisconsin randomized study of 5-FU *versus* 5-FU plus levamisole showed a statistically significant advantage for the combination (26). However, the dosage and schedule of these agents was different from that used in the successful adjuvant trials. Furthermore, only 19 of 72 patients on this study had measurable disease. Adjustment by a Cox regression model for the influence of measurable disease reduced the significance of treatment difference.

The NCCTG study in metastatic colorectal cancer was a 5-arm trial testing 5-FU against various combinations with 5-FU and included a 5-FU plus levamisole arm (20). Again, the dosage and schedule were different from those used in their subsequent adjuvant study. This study failed to demonstrate superiority of any of the combination arms over 5-FU alone. Remarkably, 5-FU in this study had a response rate of 30%, which is unusually high for 5-FU as a single agent in metastatic colorectal cancer. The Eastern Cooperative Oncology Group has reported a trial of 5-FU *versus* 5-FU plus levamisole in metastatic colorectal cancer in patients with nonmeasurable disease

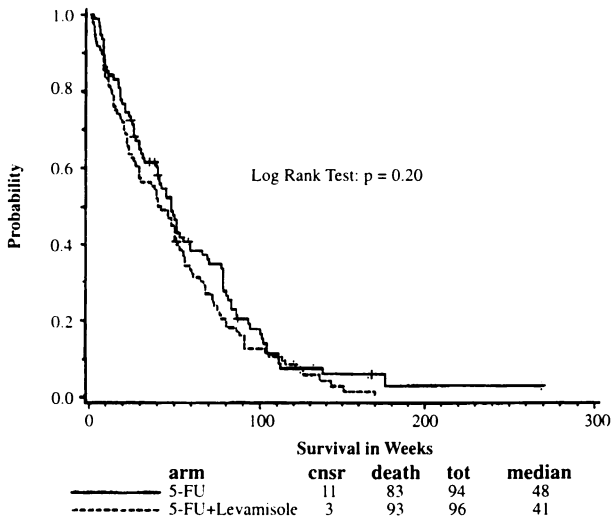

Fig. 1 Survival.

and found no benefit for the combination (27). However, this study has been reported in abstract form only, and the doses are different from those used in the NCCTG (24) and intergroup (25) studies. Therefore, in the adjuvant setting, the success of the 5-FU plus levamisole regimen in the NCCTG trial (24) was quite surprising and led to some skepticism. However, the results of the larger intergroup study (25) established 5-FU plus levamisole as standard adjuvant therapy in completely resected stage III colorectal cancer.

It is unusual for a regimen to prolong survival in the adjuvant setting and have no substantive activity in metastatic disease. This trial included patients with metastatic colorectal cancer, most of whom had good performance status. Both of the patient groups were well matched. The combination of 5-FU and levamisole failed to demonstrate any superiority over 5-FU alone in terms of response rate, duration of remission, or survival.

Another interesting aspect of this trial is the toxicity of 5-FU plus levamisole. In prior studies in colorectal cancer, levamisole has not been shown to have significant hematological toxicity, and only minor nonhematological toxicities such as mild nausea, stomatitis, and diarrhea have been reported. Treatment-related deaths were rare in these studies. Even trials that have tested the 5-FU plus levamisole combination have not reported any increase in the usual 5-FU toxicity with the combination. Longrée *et al.* (32), in their studies of adjuvant therapy in Duke's B and C colorectal cancer, found a higher incidence of grade III and i.v. granulocytopenia when levamisole was added to 5-FU. In our study, the incidence of grade 3/4 diarrhea was significantly higher in the 5-FU plus levamisole arm, and there was a trend toward higher incidence of grade 3/4 granulocytopenia as well. Treatment compliance was, however, the same as for the 5-FU arm.

This study indirectly raises questions about the role of levamisole in adjuvant therapy of colon cancer. There have been speculations that levamisole has no role at all and that the successful adjuvant studies demonstrate the effectiveness of more intense administration of 5-FU in properly selected patients (33). The NCCTG and intergroup studies of adjuvant therapy compared 5-FU plus levamisole to levamisole alone and did not include a 5-FU alone arm (24, 25). More recently, the National Surgical Adjuvant Breast and Bowel Project reported the results of their adjuvant trial comparing 5-FU plus leucovorin *versus* 5-FU plus levamisole *versus* 5-FU plus leucovorin plus levamisole (34). The 5-FU plus leucovorin arm was administered in 42-day cycles for six courses, whereas the levamisole containing arms were administered for a period of 1 year. There was a statistically significant advantage for 5-FU plus leucovorin over 5-FU plus levamisole in terms of disease-free ($P < 0.05$) and overall ($P < 0.05$) survival. The addition of levamisole did not improve the results of 5-FU plus leucovorin.

Two other trials evaluated 5-FU plus levamisole. The NCCTG evaluated 5-FU/levamisole (6 months *versus* 12 months) *versus* 5-FU/leucovorin/levamisole (6 months *versus* 12 months) and demonstrated that 6 months of 5-FU/levamisole was inferior to 6 months of 5-FU/leucovorin/levamisole (35). The Eastern Cooperative Oncology Group evaluated several different regimens, including high *versus* low dose leucovorin plus 5-FU and 5-FU/levamisole and 5-FU/levamisole/leucovorin. Six months of 5-FU + leucovorin was equivalent, if not superior to, 12 months of 5-FU + levamisole, and the addition of levamisole to 5-FU + leucovorin did not provide any additional benefit (36).

In conclusion, this cooperative group failed to demonstrate any advantage to the addition of levamisole to 5-FU in the treatment of metastatic colorectal cancer. The role, if any, of levamisole in Duke's C colorectal cancer is further questioned by this negative study in metastatic disease.

APPENDIX

Study Participants:
Arnett Clinic, Lafayette, IN;
Ball Memorial Hospital, Muncie, IN;
Community Hospitals, Indianapolis, IN;
Consultants in Blood Disorders and Cancer, Louisville, KY;
Lewis Domke, M.D., Merrillville, IN;
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Ray Drasga, M.D., Merrillville, IN;
Elkhart Clinic, Elkhart, IN;
Edward Fox, M.D., Evansville, IN;
Fort Wayne Hematology/Oncology, Fort Wayne, IN;
Galesburg Clinic, Galesburg, IL;
Georgia Hematology/Oncology, Atlanta, GA;
Alan Grosbach, M.D., Shreveport, LA;
Indiana University, Indianapolis, IN;
Johnson Memorial Hospital, Franklin, IN;
Thomas Lutz, M.D., Evansville, IN;
Memorial Hospital, South Bend, IN;
Methodist Hospital, Indianapolis, IN;
St. Vincent's hospital, Indianapolis, IN; and
Washington University, St. Louis, MO.

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