Eur J Cancer, Vol. 28A, No. 11, pp. 1817–1820, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00


# Prognostic Factors in Patients with Metastatic Colorectal Cancer Receiving 5-Fluorouracil and Folinic Acid

Joyce Steinberg, Charles Erlichman, Tahany Gadalla, Sheldon Fine and Alfred Wong

**We have reported that 5-fluorouracil (5-FU) and folinic acid increased response rate and survival in patients with metastatic colorectal cancer. Now we have analysed prognostic factors for response, toxicity, survival and time to progression. The variables used for survival and response were treatment centre, treatment, age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), site of disease, previous radiotherapy, site of primary, disease-free interval, initial alkaline phosphatase (AP), albumin (A), lactate dehydrogenase (LDH) and aspartate aminotransferase (SGOT). The significant independent variables for survival were PS of 2 or more, initial albumin and SGOT, and treatment received, in order of importance. The relative risk of death when patients received 5-FU/folinic acid was 60% of that of patients receiving 5-FU alone. The variables predictive of response were treatment and PS. The variables used for analysis of toxicity were age, treatment centre, treatment, sex, tumour response, PS, number of courses, SGOT, AP and albumin. Treatment was found to be predictive of toxicity. Thus, baseline albumin and SGOT, and 5-FU/folinic acid treatment are significant determinants of survival, 5-FU/folinic acid and PS of 2 or more are major determinants of response and no clinical parameter could be identified as a predictor of toxicity.**
*Eur J Cancer*, Vol. 28A, No. 11, pp. 1817–1820, 1992.

## INTRODUCTION

CARCINOMA OF the large bowel is a common cause of morbidity and mortality in North America. This accounted for approximately 150 000 new cases in the United States in 1989. One-half of these patients will die from metastatic disease. Although prognostic variables in the primary treatment of colorectal cancer have been identified and are used in the design of clinical trials and patient management, prognostic factors in patients with metastatic colorectal cancer are poorly defined. We and others [1–4] have previously demonstrated that the combination of 5-fluorouracil (5-FU) and folinic acid (FA) is superior to 5-FU alone. However, response rates of 30–50% mean that 50–70% of patients treated with 5-FU and FA do not respond, and this treatment has not been associated with long-term survival. The toxicity of this treatment is greater than 5-FU when used alone at the same doses and in some patients toxicity can be severe or life-threatening. As such, identification of patients who are more likely to benefit from therapy or those more likely to develop toxicity would be an important step in selecting the patient population to treat.

We describe the results of a prognostic factor analysis in patients with metastatic cancer treated in a controlled clinical trial comparing 5-FU to 5-FU plus FA [1]. The prognostic factors of survival, time to disease progression, tumour response and toxicity were evaluated in this analysis.

Correspondence to C. Erlichman.
J. Steinberg and C. Erlichman are at the Department of Medicine; T. Gadalla is at the Department of Biostatistics, Princess Margaret Hospital, 500 Sherbourne Street, Toronto, Ontario, Canada M4X 1K9; S. Fine is at the Credit Valley Hospital, 2300 Eglinton Avenue West, Mississauga, Ontario, Canada L5M 2V8; and A. Wong is at the Tom Baker Cancer Clinic, 1331 29th Street N.W., Calgary, Alberta, Canada T2N 4N2.
Revised 13 Jan. 1992; accepted 17 Mar. 1992.

## PATIENTS AND METHODS

Between March 1984 and March 1986, 130 patients with measurable recurrent or metastatic colorectal cancer were randomised to 5-FU daily 370 mg/m$^2$/day × 5 intravenously [1] with escalation to toxicity, or 5-FU 370 mg/m$^2$/day × 5 intravenously combined with FA 200 mg/m$^2$/day × 5 intravenously [1]. Patients were entered from two centres, The Princess Margaret Hospital (PMH), Toronto, Canada and The Tom Baker Clinic (TBC), Calgary, Canada. The two study groups were comparable for the following 11 clinical characteristics: Eastern Cooperative Oncology Group (ECOG) performance status (PS), age, weight loss, distribution of disease site at the time of entry to study, prior radiation, time elapsing before first metastases or recurrence, baseline serum albumin, alkaline phosphatase, aspartate aminotransferase (SGOT), lactate dehydrogenase (LDH) or sex. Complete records available for 121 patients were used in the analysis. The variables used in the prognostic factor analysis for survival, time to disease progression and tumour response were: (1) treatment centre; (2) treatment arm; (3) patients' age; (4) sex; (5) PS; (6) disease sites at randomisation; (7) prior radiation; (8) site of primary; (9) disease-free interval before randomisation; (10) SGOT at randomisation; (11) AP at randomisation; (12) LDH at randomisation; and (13) serum albumin at randomisation.

The variables selected as predictors of drug toxicity—diarrhoea, stomatitis and neutropenia—were: (1) treatment centre; (2) treatment arm; (3) sex; (4) tumour response; (5) PS; (6) age; (7) body weight at entry; (8) SGOT at randomisation; (9) AP at randomisation; (10) serum albumin at randomisation; and (11) no. of courses received. Stepwise regression using both forward selection and backward elimination was used in the analysis. Cox proportional hazard model was utilised with survival and time to disease progression as outcome variables [5]. Stepwise

*Table 1. ECOG performance status distribution according to centre and treatment*

| | Performance status | | | |
|---|---|---|---|---|
| | 0 | 1 | 2 and 3 | Total |
| Arm 1 (5-FU only) | 19 | 37 | 5 | 61 |
| Arm 2 (5-FU + FA) | 19 | 41 | 4 | 64 |
| PMH | 0 | 75 | 8 | 83 |
| TBC | 38 | 3 | 1 | 42 |
| Total | 38 | 78 | 9 | 125 |

PMH, Princess Margaret Hospital.
TBC, Tom Baker Clinic.

logistic regression was used to identify prognostic factors significant for tumour response. The $\chi^2$-test was used to examine for possible association between age group and toxicity.

## RESULTS

130 patients were randomised on the study. 5 were inevaluable due to refusal of treatment or did not meet eligibility criteria. Baseline serum albumin was missing for 4 patients, therefore complete records from 121 patients were used in this analysis. The PS of patients on trial according to treatment centre and treatment arm are summarised in Table 1. The majority of patients on study had a good performance status and those treated at Tom Baker Clinic were predominantly PS 0.

*Prognostic factors influencing survival*

The four variables predicting survival in decreasing order of importance when using the forward selection model were: (1) PS $\geq 2$ ($P < 0.0001$); (2) initial serum albumin ($P < 0.0001$); (3) initial SGOT ($P = 0.005$); and (4) treatment received ($P = 0.0251$). Using the backward elimination model, the following six variables were obtained: (1) PS $\geq 2$ ($P < 0.0001$); (2) initial serum albumin ($P < 0.0001$); (3) initial SGOT ($P = 0.005$); (4) treatment received ($P = 0.014$); (5) PS = 1, ($P = 0.0307$); and (6) treatment centre ($P = 0.046$).

The risk of death decreased with increasing initial serum albumin but increased with increased initial SGOT. Based on the backward elimination model, under the proportional hazard assumption, the relative risk of death in the combination group was 60% of that observed in patients receiving 5-FU alone.

*Prognostic factors predicting time to disease progression*

Both forward selection and backward elimination gave the same regression model when predicting time to disease progression. The following four variables were found to be statistically significant: (1) baseline serum albumin ($P = 0.0003$); (2) PS $\geq 2$ ($P = 0.0023$); (3) PS = 1 ($P = 0.0018$); and (4) treatment arm ($P = 0.0275$).

Risk of disease progression decreased with increasing initial serum albumin and increased with worsening PS. The relative risk of disease progression in the combination treatment arm was 2/3 that observed in the single-agent group. Baseline AP and SGOT were significant as univariate variables, but lost their significance when albumin was entered into the regression model. Treatment centre was significant as a univariate variable, but lost its significance when PS entered the regression model. Although the data revealed a significant difference in the distribution of PS between the two treatment centres ($\chi^2 = 108.1$, $P < 0.0001$, Table 1), the two treatment arms were balanced for this variable.

*Prognostic factors for tumour response*

The variables mentioned, plus two additional variables, were investigated as potential predictors of tumour response. These additional variables were changes in the value of SGOT and AP after the first course of treatment. The inclusion of these two variables reduced the no. of patients with complete records to 102. 19 patients had missing values for SGOT and/or AP after the first course of treatment. Using stepwise logistic regression, the treatment arm was a highly significant predictor for tumour response ($P < 0.0001$). None of the other variables, including changes in SGOT or AP, added significance.

Excluding the covariates of changes in SGOT and AP, the analysis was repeated on the data from the 121 patients with complete records. The data from all patients with PS $\geq 2$ was included in the analysis. Treatment received was again found to be highly significant ($P \leq 0.0001$). In this analysis, having a PS of 2 or 3 added significant improvement to the predictive ability of the regression model ($P = 0.0473$). None of the 9 patients with PS $\geq 2$ responded, regardless of treatment.

*Duration of response*

The 24 responders were used for this analysis. The covariates of treatment, PS and initial albumin were used as potential predictors for duration of response in the analysis. Only PS [0 vs. 1] was found to be significant ($P = 0.0033$). Median duration of response for patients with PS = 0 ($n = 8$) was 8.5 months, while for patients with PS = 1 ($n = 17$) was 4.3 months.

*Toxicity*

The factors identified previously were tested as the possible predictors for toxicity. Toxicity was defined as diarrhoea, stomatitis on a graded scale [1] and neutropenia. Grades 2 and 3 were considered as toxicity and grade 1 was classified as no toxicity in this analysis. Only the treatment arm was found to be significantly associated with toxicity. The patients receiving combination treatment experienced more diarrhoea, stomatitis and lower median nadir neutrophil counts. The $\chi^2$-test was used in the analysis of the association of age group and toxicity. Age was divided into 10-year groups. No significant association was found. Table 2 summarises variables significant in predicting outcome parameters selected for this analysis.

## DISCUSSION

The natural history of metastatic colorectal cancer is variable, with the median survival for patients with untreated liver metastases ranging from 6 to 8 months [6–8]. Many patients with metastatic colorectal carcinoma now receive palliative treatment for control of tumour growth and symptoms. Thus, it is important to identify prognostic factors for outcome which will aid in the design of clinical trials, interpretation of therapeutic results, and treatment decisions in the clinical setting.

Analysis of our patients with metastatic colorectal cancer entered into a randomised trial comparing 5-FU to 5-FU plus FA enabled us to identify patient and treatment variables which were significant in the prediction of survival, time to disease progression, tumour response, duration of response and toxicity (Table 2). Using both forward and backward elimination methods, we found survival to be dependent upon PS $\geq 2$,

*Table 2. Variables predicting outcome*

| Dependent parameter | Independent parameter* | | |
|---|---|---|---|
| | Forward selection | | Backward elimination |
| 1. Survival | PS ≥ 2 | − | PS ≥ 2 |
| | Initial albumin | + | Initial albumin |
| | Initial SGOT | − | Initial SGOT |
| | 5-FU + FA therapy | + | 5-FU + FA therapy |
| | | − | PS = 1 |
| | | − | Treatment centre (TBC) |
| | Forward selection and backward elimination | | |
| 2. Time to disease progression | Initial albumin | + | |
| | PS ≥ 2 | − | |
| | PS = 1 | − | |
| | 5-FU + FA therapy | + | |
| 3. Tumour response | 5-FU + FA therapy | + | |
| | PS ≥ 2 | − | |
| 4. Duration of response | | | |
| | PS = 1 | − | |
| 5. Toxicity (GI, stomatitis and neutropenia) | 5-FU + FA therapy | + | |

*Ranked in order of decreasing significance ($P < 0.05$).
+ = positive impact.
− = negative impact.

initial albumin, initial SGOT and treatment received. The backward elimination model confirmed these variables as significant. The identification of PS of 0 or 1 as a predictor indicates that among patients with a PS of 0 or 1, patients with a performance status of 0 have significantly longer survival than patients with a PS of 1. This is consistent with the data of the Mayo Clinic, the North Central Cancer Treatment Group and the Nordic Gastrointestinal [2, 9, 10]. The identification of treatment centre as a weak prognostic indicator independent of the PS differences at the two treatment centres suggests that there are other elements influencing survival that cannot be determined from this analysis. However, the contribution of this factor to survival is small ($P = 0.046$). PS ≥ 2 was a negative predictor for survival, time to disease progression, tumour response and duration of response. None of the patients with a PS ≥ 2 responded to treatment.

SGOT and albumin at randomisation were significant predictors of survival and albumin was the most significant predictor for time to disease progression. These measures may be a reflection of overall tumour burden. Treatment with 5-FU plus FA was an important independent predictor of four of the five dependent variables (Table 2). Even when biological parameters were accounted for, treatment with 5-FU plus FA increased survival, time to disease progression, tumour response, duration of response and toxicity. The relative improvement with 5-FU plus FA in response and survival when compared with that of 5-FU alone is greater, suggesting that the therapeutic index is enhanced despite the increased toxicity. This interpretation of these results is supported by the study of Valone *et al.* [11], in which was demonstrated a similar response in patients receiving 5-FU administered at high-dose intensity or 5-FU plus FA, but with the occurrence of greater toxicity in the 5-FU arm.

Others have analysed cohorts of patients retrospectively and identified additional prognostic variables in patients with metastatic colorectal carcinoma. PS was found to be a significant predictor of survival [12–15] but did not consistently predict response [13]. Additional prognostic indicators of survival have been proposed, including weight loss in the presence of metastatic diseases [12, 15, 16], laboratory chemistry and blood counts [6, 7, 13, 17–19], the presence of liver metastases or the extent of liver involvement [8, 13, 15, 16,20]. Albumin and SGOT were the only laboratory parameters found to be predictors of survival in our study population. Other potential markers of treatment outcome which were not available in our study population may contribute to management of patients with colorectal cancer. Measures of tumour proliferation, ploidy, growth factor receptors and p53 are being evaluated currently. These may become important in future clinical trial design and patient management.

Further prospective randomised trials are needed to improve treatment strategies for patients with metastatic colorectal carcinoma. We have identified prognostic variables which predict for survival, time to progression and response. Patients with a normal albumin and SGOT are more likely to live longer. Patients with PS ≥ 2 have a poor survival and are less likely to respond to 5-FU plus FA. The consideration of these factors as stratification variables in future clinical trials will aid in identifying clinical measurements whereby treatment decisions are made in patients with metastatic colorectal cancer.


1. 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**, 469–475.
2. 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, 1407–1417.
3. Petrelli N, Herrera L, Rustum Y, *et al.* A prospective randomized trial of 5-fluorouracil versus 5-fluorouracil and high dose leucovorin versus 5-fluorouracil and methotrexate in previously untreated patients with advanced colorectal carcinoma. *J Clin Oncol* 1987, 5, 1559–1565.
4. 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, 1419–1426.
5. Cox D. Regression models and life tables. *J R Statist Soc* 1972, **B3**, 187–220.
6. Lahr CJ, Soong S-J, Cloud G, *et al.* A multifactorial analysis of prognostic factors in patients with liver metastases from colorectal carcinoma. *J Clin Oncol* 1983, **1**, 720–726.
7. Bengmark S, Hafström L. The natural history of primary and secondary malignant tumors of the liver. *Cancer* 1969, **23**, 198–202.
8. Bengtsson G, Carlsson G, Hafström L, *et al.* Natural history of patients with untreated liver metastases from colorectal cancer. *Am J Surg* 1981, **141**, 586–589.
9. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *Cancer* 1989, **63**, 1026–1030.
10. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Superiority of sequential methotrexate, fluorouracil and leucovorin to fluorouracil alone in advanced symptomatic colorectal carcinoma: a randomized trial. *J Clin Oncol* 1989, 7, 1437–1446.
11. 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 California oncology group. *J Clin Oncol* 1989, 7, 1427–1436.

12. Laven P, Mittelman A, Douglass H, Engstrom P, Klaassen D. Survival and response to chemotherapy for advanced colorectal adenocarcinoma. *Cancer* 1980, **46**, 1536–1543.
13. Kemeney N, Braun DW. Prognostic factors in advanced colorectal carcinoma. *Am J Med* 1983, **74**, 786–794.
14. Edler L, Heim ME, Quintero C, Brummer T, Queisser W. Prognostic factors of advanced colorectal cancer patients. *Eur J Cancer Clin Oncol* 1986, **22**, 1231–1237.
15. Goslin R, Steele G, Zamcheck N, Mayer R, MacIntyre J. Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon or rectum. *Dis Colon Rectum* 1982, **25**, 749–754.
16. Finan PJ, Marshall RJ, Cooper EH, Giles GR. Factors affecting survival in patients presenting with synchronous hepatic metastases from colorectal cancer: a clinical and computer analysis. *Br J Surg* 1985, **72**, 373–377.
17. DeBraun LM, Van De Velde CJH, Bouwhuis-Hoogerwerf ML, Zwaveling A. Diagnostic evaluation and survival analysis of colorectal cancer patients with liver metastases. *J Surg Oncol* 1987, **34**, 81–86.
18. Bedikian AY, Chen TT, Malahy M, Patt YZ, Bodey GP. Prognostic factors influencing survival of patients with advanced colorectal cancer: hepatic artery infusion versus systemic intravenous chemotherapy for liver metastases. *J Clin Oncol* 1984, **2**, 174–180.
19. Tartter PI. Pretreatment prognostic factors in colorectal cancer patients with synchronous liver metastases. *Eur J Surg Oncol* 1987, **13**, 485–491.
20. Wood CB, Gillis CR, Blumgart LH. A retrospective study of the natural history of patients with liver metastases from colorectal cancer. *Clin Oncol* 1976, **2**, 285–288.

*Eur J Cancer, Vol. 28A, No. 11, pp. 1820–1823, 1992.*
*Printed in Great Britain*

*0964–1947/92 $5.00 + 0.00*


# Phase II Trial of 5-Fluorouracil and Recombinant Interferon Alfa-2B in Metastatic Colorectal Carcinoma

**Hans Josef Weh, Dieter Platz, Dietrich Braumann, Peter Buggisch, Nils Eckardt, Wolff Helmut Schmiegel, Siegfrid Drescher, Ulrich Richard Kleeberg, Ulrich Müllerleile, Wolfgang Crone-Munzebrock, Rüdiger Hoffmann, Peter Müller, Rainer Klapdor, Rainer Pompecki, Heinrich Erdmann, Lutz Reichel, M. Jungbluth, Lutz Hoffmann, Klaus Mainzer and Dieter Kurt Hossfeld**

**Between February 1990 and April 1991, 59 previously untreated patients with progressive and/or symptomatic metastatic colorectal carcinoma were enrolled in a phase II study of 5-fluorouracil (5-FU) and interferon alfa-2b (IFN-α). 5-FU 750 mg/m²/day was administered as continuous infusion for 5 days, then weekly in a dose of 750 mg/m² as intravenous push injection starting on day 15. IFN-α 9 MU was given subcutaneously three times a week. Treatment was given for a maximum of 6 months. 55 patients are evaluable for response and 51 for toxicity. 17 patients (31%) achieved a partial remission, 15 (27%) had stable disease and 21 patients (38%) had progressive disease. Median duration of remission was 5 months and median survival for all patients 10 months. Toxicity was important with two treatment-related deaths and severe leukopenia, fever, diarrhoea and mucositis in about one third of the patients. In our opinion, this regimen is effective but rather toxic in metastatic colorectal carcinoma.**
*Eur J Cancer*, Vol. 28A, No. 11, pp. 1820–1823, 1992.

## INTRODUCTION

METASTATIC COLORECTAL carcinoma remains a major challenge. Wadler *et al.* [1, 2] reported high remission rates of 76 and 63%, respectively, in 17 and 32 previously untreated patients with advanced colorectal carcinoma, using a combination of interferon α-2a (IFN-α) and 5-fluorouracil (IFN-α/5-FU). Stimulated by these results, in February 1990 a group of oncologists in Hamburg working both in hospitals and private practice started a confirmatory phase II study in patients with metastatic colorectal carcinoma using the same regimen as applied by Wadler *et al.*

## PATIENTS AND METHODS

Between February 1990 and April 1991, 59 patients with metastatic colorectal carcinoma entered the study. The main inclusion criteria were: histologically proven metastatic colorectal carcinoma; no possibility of surgical therapy with curative intention; bidimensionally measurable disease; no prior chemotherapy; documented progressive disease and/or symptomatic disease; Karnofsky performance status ≥50% (ECOG 0–2); adequate bone marrow function with a white blood cell (WBC)count >3000/μl and a platelet count >100 × $10^3$/μl, adequate renal function with a serum creatinine level <2.0 mg/dl