Protracted Treatment with Tegafur and Low Dose Oral Leucovorin in Patients with Advanced Colorectal Carcinoma

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BACKGROUND. Protracted oral administration of tegafur (TG) and leucovorin (LV) attempts to simulate the continuous infusion of 5-fluorouracil, with a higher intracellular folate pool. In a prior dose-finding study with a fixed TG dose of 0.75 g/m^2/day for a period of 21 days and continuous oral LV, the recommended dose of LV was 45 mg/day in 28-day cycles.

METHODS. Thirty-nine patients with histologic confirmation of adenocarcinoma of the colon or rectum, either advanced or metastatic disease, and who were not candidates for radical treatment were included in a Phase II study using this schedule.

RESULTS. One hundred sixty-three cycles of chemotherapy were delivered (median, 4 cycles per patient). Toxicity was observed in the form of diarrhea, which was severe in 12 patients (30.7%). Grade 3 (according to the World Health Organization criteria) oral mucositis was recorded in 7 patients (18%). Asthenia was severe in 10% of the patients. Recuperation from toxicity was rapid and managed primarily on an outpatient basis. Two complete (5.1%) and 13 partial (33.3%) responses were observed, with a global response index of 38.5% (95% confidence interval, 23.2–53.6%). The median overall survival was 11.3 months.

CONCLUSIONS. The results of this study show that an all-oral regimen of tegafur and leucovorin can obtain biochemical modulation, with a significant response rate, in patients with advanced colorectal carcinoma. Randomized trials are needed to assess the possible advantage of this regimen over intravenous schedules. ***Cancer* 1998;83:254–8.** © *1998 American Cancer Society.*

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The best available therapy for advanced colorectal carcinoma is capable of achieving only a 20–40% objective remission rate with marginal improvement in survival. 5-fluorouracil (5-FU) is the most studied drug in this setting and its biochemical modulation with leucovorin (LV) consistently shows more activity than 5-FU alone.[1]

The factors that affect this biochemical modulation depend on the dose, treatment schedule, and method of folate administration and can vary between patients and between neoplasms. Therefore, more than 10 years after the publication of the first study of 5-FU modulated with folinic acid, there is still no optimal treatment schedule.

Tegafur (TG) is a highly lipophilic prodrug that is slowly metabolized into 5-FU in vivo[2] and has practically complete oral bioavailability, with a serum half-life of 10 hours.[2] Phase I studies recommend a 1 g/m^2/day dose by continuous oral administration, with diarrhea being the toxic limitation of the dose.[2] In controlled studies, TG achieved response rates, mean duration of response, and survival

similar to intravenous 5-FU in patients with advanced colorectal carcinoma.[3–5] Protracted administration of oral TG comes closest to reproducing the pharmacokinetics of true 5-FU infusions. Biochemical modulation of TG by oral folinic acid is an attractive approach to increase its efficacy. Furthermore, oral administration of folinic acid may have some pharmacokinetic advantages and repeated low doses of folinic acid could provide sufficient concentration to modulate the action of 5-FU.[6]

In a previous dose-finding study with a fixed TG dose of 0.75 g/m^2/day for 21 days and oral folinic acid at different levels (15, 30, 45, 60, and 90 mg/day) in 28-day cycles, we observed a statistically linear correlation between folinic acid dose and an increase in toxicity to a plateau of 60 mg of folinic acid daily. The recommended dose of folinic acid for the dose of TG given earlier was 45 mg/day in Phase II studies.[7]

Given this background, we conducted a Phase II study of oral TG and folinic acid in patients with advanced or metastatic colorectal carcinoma, with the goal of analyzing the efficacy and confirming the toxic profile of this schedule. This study used the doses of TG and oral folinic acid suggested in the aforementioned Phase I trial. The main advantage expected of an all-oral regimen of biochemical modulation was avoiding the need for frequent administration of intravenous treatment associated with the use of 5-FU and folinic acid.

PATIENTS AND METHODS

Eligible patients had histologically confirmed colorectal adenocarcinoma (CRC), advanced or metastasic disease, were not candidates for radical treatment, were age < 75 years, and had a Karnofsky index of $\geq 60\%$, a life expectancy > 3 months, bidimensionally measurable disease, adequate bone marrow reserve as well as normal hepatic and renal function (except secondary to tumoral invasion), and the ability to maintain adequate oral intake. No patient was to have received previous chemotherapy for metastasic disease, radiotherapy for the measurable disease studied, or have received adjuvant chemotherapy within the preceding 12 months. All patients were informed before a witness of the objectives of the study and informed consent was obtained.

Therapeutic Plan

The treatment schedule, which was administered on an outpatient basis, was comprised of 0.75 g/m^2 of oral TG daily (capsules contain 400 mg of TG, so daily doses were rounded to the nearest multiple according to body surface area) administered in 2 or 3 doses after meals (depending on the total dose) for 21 consecutive days in 28-day cycles. Folinic acid was administered continuously (15 mg orally every 8 hours). Patients experiencing World Health Organization Grade 1–2 toxicity received symptomatic treatment and no dose reduction of TG. In patients developing severe toxicity (Grade 3–4), TG was suspended until the complete resolution of the symptoms and treatment could be reinitiated, according to clinical criteria, with a 25% dose reduction in subsequent cycles. Patients with Grade 3 toxicity after dose reduction were removed from the study. Treatment was maintained until disease progression or unacceptable toxicity, up to a maximum of six cycles.

Assessment of Results

All patients receiving one cycle were considered evaluable for response and toxicity. Physical examination and biochemical tests were performed after each cycle and an evaluation of all measurable lesions was performed every two cycles. After treatment, physical examination, biochemical tests, and imaging evaluation were performed every 2 months. Response and toxicity were recorded according to the WHO criteria.[8] A complete clinical response was comprised of the disappearance of all measurable tumor during at least a 4-week period. A partial response required a decrease of $> 50\%$ in the largest perpendicular dimensions of the most representative lesions (initial minimum dimension of 2 cm) without an increase in the size of the remaining lesions or the appearance of new lesions for at least 4 weeks. Stabilization was defined as a decrease in size of $< 50\%$ or an increase of $< 25\%$ in the most representative lesions without the appearance of new lesions for at least 4 weeks. Progressive disease was defined as the appearance of new lesions or a $>$ 25% increase in any existing lesion. Toxicity was recorded on a monthly basis and evaluated according to the WHO recomendations. Neurologic toxicity in the form of fatigue was evaluated according to the criteria established for interferon : 0: none, 1: mild, 2: moderate, 3: severe, and 4: intense.[9]

Statistical Methods

Wilcoxon rank sum statistics were used to compare quantitative variables and the chi-square test was used for percentages. Survival was measured from the initiation of therapy using the Kaplan-Meier method. The progression free interval was defined as the period between treatment onset and the first documentation of tumor progression.

RESULTS

From November 1993 to November 1995, 39 patients with advanced CRC were evaluated for response and

TABLE 1
Patient Characteristics

	No.	(%)
Gender		
Male	25	(64.1)
Female	14	(35.9)
Mean age (yrs) (range)	59.7	(37–75)
Location of primary tumor		
Colon	26	(66.7)
Rectum	13	(33.3)
Karnofsky index		
60–70	8	(20.5)
80–90	22	(56.4)
100	9	(23.1)
Previous complementary chemotherapy	8	(20.5)
No. of metastatic sites		
1	16	(41)
2	13	(33.3)
≥3	10	(25.7)
Location of disease		
Primary tumor	17	(43.6)
Peritoneum	6	(15.4)
Liver	28	(71.8)
Lymph nodes	8	(20.5)
Lung	12	(30.8)
Other	2	(5.1)
Median CEA (ng/dL) (range)	109.3	(2–968)

CEA: carcinoembryonic antigen.

TABLE 2
Toxicity of 163 Cycles

	WHO Grade 1–2		WHO Grade 3–4	
	Per patient No. (%)	Per cycle No. (%)	Per patient No. (%)	Per cycle No. (%)
Diarrhea	6 (15.4)	22 (13.5)	12 (30.8)	14 (8.5)
Mucositis	15 (38.5)	25 (15.3)	7 (17.9)	8 (4.9)
Fatigue	14 (35.9)	40 (24.5)	4 (10.3)	4 (2.5)
Nausea and emesis	8 (20.5)	14 (8.6)	2 (5.1)	2 (1.2)
Hematologic	7 (17.9)	11 (6.7)	—	—
Skin	12 (30.7)	15 (9.2)	1 (2.6)	1 (0.6)
Conjunctivitis	4 (10.2)	4 (2.5)	—	—

WHO: World Health Organization.

toxicity. The main patient characteristics are listed in Table 1. The metastasic site was unique in 41% of the patients and there were ≥ 3 sites in 25% of patients. Hepatic involvement was the most frequent metastatic distribution (72%), and was multiple in 50% of the patients. Only one patient had an unresectable, locally advanced tumor as a unique site of disease. The mean carcinoembryonic antigen value was 109 ng/dL (range, 2–968 ng/dL). These values reflect the high tumoral load of the patients included in this study.

A total of 163 cycles of treatment were administered, with a median of 4 cycles per patient (range, 1–6 cycles). Nineteen patients (49%) received the maximum planned treatment of 6 cycles.

Toxicity principally was in the form of diarrhea, observed in 9% of the cycles and in 18 of 39 patients, being severe in 12 patients (30.7%) (Table 2). There was a greater incidence of oral mucositis, presenting in 20% of the cycles and in 22 patients; it was Grade 3 in 7 patients (18%) and 5% of the cycles. Asthenia was severe in 10% of patients. Mild cutaneous toxicity was registered in the form of hand-foot syndrome in 30% of patients. Hematologic and hepatic toxicity was minimal. A dose reduction was required for 15 of 39 patients (38.5%), but in only 2 patients was treatment suspended due to toxicity (one case due to myocardial ischemia and the other due to hemolytic syndrome). Grade 4 toxicity was observed in only six patients, all with Grade 4 diarrhea requiring hospitalization. There were no deaths due to toxicity.

Two complete responses (5.1%) (both in patients with lung metastases) and 13 partial responses (33.3%) were observed, with a global response rate of 38.4% (95% confidence interval, 23.2–53.6%). The mean number of cycles to achieve a response was two (range one to six cycles). Stabilization was achieved in 12 patients (30.8%) and disease progression occurred in 12 other patients (30.8%). There were no significant differences between the various clinical factors analyzed and response.

The median global survival was 11.3 months. In patients with an objective response, the median survival was 24.4 months, in patients with stable disease the median survival was 11.3 months, and in those with disease progression the median survival was 3.3 months ($P < 0.001$). The median time to progression was 7.6 months in patients with a response and 7.5 months in patients with stabilization. At 12 months 41% of the patients were still alive, and at 24 months 18% were still alive. Two patients were long term survivors.

DISCUSSION

To our knowledge, the intravenous modulation schedules for 5-FU with LV are the most studied and have the most consistent results. Therefore a meta-analysis of 5-FU modulation with LV shows significant differences in terms of the objective rate of response (23% vs. 11%) when compared with 5-FU alone.[1]

The results of randomized trials comparing high LV doses versus low LV doses[10–14] led us to believe that the LV dosage by itself has less significance in the biochemical modulation of 5-FU. The grade and ex-

tent of the biochemical modulation of the fluoropyrimidines by LV depend in large part on the formation of polyglutamates of 5,10 methylenetetrahydrofolate. The larger the chain of polyglutamates, the more active the modulation. Based on in vitro data, the formation of polyglutamates appears related to the duration of exposure to LV.[15]

Conversely, the slow rate of growth of colorectal carcinoma, together with the very short serum half-life of 5-FU and its specificity of action in the S-phase of the cell cycle supposes that only a small part of the neoplastic cells will be susceptible to each administration of 5-FU in bolus. This is the rationale for the administration of 5-FU in continuous infusion. Continuous, protracted 5-FU infusion treatment schedules have been demonstrated to be superior to shorter administration schedules.[16,17]

In agreement with our working hypothesis, in an excellent review of the clinical factors that can optimize the biochemical modulation of 5-FU by LV, Etienne et al[18] recommended protracted exposure to 5-FU and LV as an optimal means of biochemical modulation. The administration of low dose oral TG and LV, but in a continuous manner, conforms with this recommendation. Our rates of activity achieved (overall response 38%) compare favorably with respect to intravenous modulation schedules.[1] An additional 30% of patients achieved stable disease. Therefore, a high proportion of patients with CRC received some therapeutic benefit that lasted $>$ 7 months. We speculate that a longer treatment duration may result in more prolonged benefit.

In the same manner that the data regarding the modulation activity of 5-FU with folinic acid consistently point out its superiority to 5-FU alone,[1] this increase in activity is accompanied by an increase in toxicity. The type of toxicity depends more on the schedule than the dose of LV used.

We noted an incidence of severe diarrhea in 30% of patients, a rate similar to that observed in high dosage schedules in weekly administration.[12,13,14,19] Half of these patients required hospitalization for intravenous hydration. Approximately 18% of patients had Grade 3 oral mucositis, similar to the percentage observed in intensive administration schedules.[10,12,14,19,20]

It is very important to emphasize that the correction and management of this registered toxicity was rapid in all patients, and was performed on an outpatient basis in the majority of cases. Hospital admission was required in only 15% of our patients compared with 21% in intensive schedules with low dose LV and 31% in weekly schedules with high dose LV.[14] The TG dose reduction made the administration of successive treatments in these patients possible without further complications. This explains the lower percentage of toxicity per administered cycle compared with the toxicity per patient. We did not encounter any clinical data indicating a greater risk of toxicity.

The practically nonexistent hematologic toxicity, as well as the appearance of cutaneous toxicity in the form of hand-foot syndrome in 33% of patients, is very similar to results obtained in protracted, continuous 5-FU administration.[16,19]

Whatever LV modulation schedule is used, the increase in effectiveness is achieved universally at the expense of an increase in toxicity. Our protracted administration schedule of low dose oral TG and LV reproduces a spectrum of toxicity that is common in intravenous modulation schedules. The early detection of this toxicity over the length of the cycle allows for rapid, outpatient correction in the majority of patients, allowing management to be on a largely outpatient basis.

We believe that a simple treatment schedule with oral administration can achieve results similar to more complex intravenous administration schedules, with an improvement in quality of life for these patients. To assess the possible advantage of an all-oral regimen over intravenous schedules, we have begun a randomized trial comparing our regimen with standard intravenous modulation.

REFERENCES

1. 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* 1992;10:896–903.
2. Brade WP, Herdrich K. Tegafur. A review of pharmacology and toxicology. *Contr Oncol* 1983;14:2–25.
3. Bedikian AY, Stroehlein J, Korinek J, Karlin D, Bodey GP. A comparative study of oral tegafur and intravenous 5-fluorouracil in patients with metastatic colorectal cancer. *Am J Clin Oncol* 1983;6:181–6.
4. Bjerkeset T, Fjosne HE. Comparison of oral ftorafur and intravenous 5-fluorouracil in patients with advanced cancer of the stomach, colon or rectum. *Oncology* 1986;43:212–5.
5. Andersen E, Pedersen H. Oral ftorafur versus intravenous 5-fluorouracil. A comparative study in patients with colorectal cancer. *Acta Oncol* 1987;26:433–6.
6. Schilsky RL, Choi KE, Vokes EE, Guaspari A, Guarnieri C, Whaling S, et al. Clinical pharmacology of the stereoisomers of leucovorin during repeated oral doses. *Cancer* 1989; 63(Suppl):1018–21.
7. Nogué M, Saigí E, Seguí MA. Clinical experience with tegafur and low dose oral leucovorin: a dose-finding study. *Oncology* 1995;52:167–9.
8. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981;47:207–14.
9. Creagan ET, Buckner JC, Hahn RG, Richardson RR, Schaid DJ, Kovach JS. An evaluation of recombinant leukocyte A interferon with aspirin in patients with metastatic renal cell cancer. *Cancer* 1988;61:1787–91.

10. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson LK, 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;7:1407–17.
11. Poon MA, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Tschetter LK, et al. Biochemical modulation of fluorouracil with leucovorin: confirmatory evidence of improved therapeutic efficacy in advanced colorectal cancer. *J Clin Oncol* 1991;9:1967–72.
12. Petrelli N, Douglass HO, Herrera L, Russell D, Stablein DM, Bruckner HW, 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.
13. Jäger E, Heike M, Bernard H, Klein O, Bernhard G, Lautz D, et al. Weekly high-dose leucovorin versus low-dose leucovorin combined with fluorouracil in advanced colorectal cancer: results of a randomized multicenter trial. *J Clin Oncol* 1996;14:2274–9.
14. Buroker TR, O'Connell MJ, Wieand HS, Krook JE, Gerstner JB, Mailliard JA, et al. Randomized comparison of two schedules of fluorouracil and leucovorin in the treatment of advanced colorectal cancer. *J Clin Oncol* 1994;12:14–20.
15. Rustum YM. Role of R,S-leucovorin dose and schedule in the therapeutic modulation of the efficacy and toxicity of fluoropyrimidines. Presented at: Proceedings of Leucovorin Modulation of Fluoropyrimidines, Amsterdam, the Netherlands, April 12, 1989.
16. Lokich JJ, Ahlgren JD, Gullo JJ, 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* 1989;7:425–32.
17. Rougier P, Buyse M, Ryan L, Hansen R, Zee B, Weinwrman B, et al. Meta-analysis of all trials comparing intravenous bolus administration to continuous infusion of 5-fluorouracil in patients with advanced colorectal cancer. *Proc Annu Am Soc Clin Oncol* 1997;16:A946.
18. Etienne MC, Guillot T, Milano G. Critical factors for optimizing the 5-fluorouracil-folinic acid association in cancer chemotherapy. *Ann Oncol* 1996;7:283–9.
19. Leichman CG, Fleming TR, Muggia FM, Tangem CM, Ardalan B, Doroshow JH, et al. Phase II study of fluorouracil and its modulation in advanced colorectal cancer: a Southwest Oncology Group study. *J Clin Oncol* 1995;13:1303–11.
20. Valone FH, Friedman MA, Wittlinger PS, Drakes T, Eisenberg PD, Malec M, 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; 7:1427–36.