IRINOTECAN PLUS FLUOROURACIL AND LEUCOVORIN FOR METASTATIC COLORECTAL CANCER

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ABSTRACT

Background The combination of fluorouracil and leucovorin has until recently been standard therapy for metastatic colorectal cancer. Irinotecan prolongs survival in patients with colorectal cancer that is refractory to treatment with fluorouracil and leucovorin. In a multicenter trial, we compared a combination of irinotecan, fluorouracil, and leucovorin with bolus doses of fluorouracil and leucovorin as first-line therapy for metastatic colorectal cancer. A third group of patients received irinotecan alone.

Methods Patients were randomly assigned to receive irinotecan (125 mg per square meter of body-surface area intravenously), fluorouracil (500 mg per square meter as an intravenous bolus), and leucovorin (20 mg per square meter as an intravenous bolus) weekly for four weeks every six weeks; fluorouracil (425 mg per square meter as an intravenous bolus) and leucovorin (20 mg per square meter as an intravenous bolus) daily for five consecutive days every four weeks; or irinotecan alone (125 mg per square meter intravenously) weekly for four weeks every six weeks. End points included progression-free survival and overall survival.

Results Of 683 patients, 231 were assigned to receive irinotecan, fluorouracil, and leucovorin; 226 to receive fluorouracil and leucovorin; and 226 to receive irinotecan alone. In an intention-to-treat analysis, as compared with treatment with fluorouracil and leucovorin, treatment with irinotecan, fluorouracil, and leucovorin resulted in significantly longer progression-free survival (median, 7.0 vs. 4.3 months; $P=0.004$), a higher rate of confirmed response (39 percent vs. 21 percent, $P<0.001$), and longer overall survival (median, 14.8 vs. 12.6 months; $P=0.04$). Results for irinotecan alone were similar to those for fluorouracil and leucovorin. Grade 3 (severe) diarrhea was more common during treatment with irinotecan, fluorouracil, and leucovorin than during treatment with fluorouracil and leucovorin, but the incidence of grade 4 (life-threatening) diarrhea was similar in the two groups (<8 percent). Grade 3 or 4 mucositis, grade 4 neutropenia, and neutropenic fever were less frequent during treatment with irinotecan, fluorouracil, and leucovorin. Adding irinotecan to the regimen of fluorouracil and leucovorin did not compromise the quality of life.

Conclusions Weekly treatment with irinotecan plus fluorouracil and leucovorin is superior to a widely used regimen of fluorouracil and leucovorin for metastatic colorectal cancer in terms of progression-free survival and overall survival. (N Engl J Med 2000;343:905-14.)

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THE antimetabolite fluorouracil is widely used to treat metastatic colorectal cancer, the second-leading cause of death from cancer in North America.[1] The drug inhibits thymidylate synthase, an enzyme required for the synthesis of DNA.[2] It is commonly administered with leucovorin, a reduced folate (tetrahydrofolate) that increases the affinity of fluorouracil for thymidylate synthase. Among various schedules of administration, the efficacy of the Mayo Clinic bolus regimen, in which the two drugs are injected daily for five days every four weeks, has been validated in randomized trials[3-5] and is frequently used as first-line therapy for metastatic colorectal cancer.

Irinotecan (Camptosar, Pharmacia) is a potent inhibitor of topoisomerase I, a nuclear enzyme involved in the unwinding of DNA during replication.[6-8] Irinotecan has demonstrated antitumor activity against metastatic colorectal cancer when used alone as first-line treatment[9-12] or as second-line treatment after the failure of fluorouracil.[10-18] In randomized phase 3 trials, second-line irinotecan extended survival significantly as compared with supportive care[19] or infusions of fluorouracil and leucovorin as a second-line therapy.[20]

The mechanism of action of irinotecan and its activity against untreated and fluorouracil-resistant colorectal cancer were the rationale for combining irinotecan with fluorouracil and leucovorin as first-line therapy for this disease. A phase 1 study[21] developed a combination regimen based on the weekly irinotecan schedule that had been the most widely studied in the United States.[9,11,13,14,16,18,22] We conducted a phase 3 trial in which the combination of irinotecan, fluorouracil, and leucovorin was compared with the Mayo Clinic bolus regimen of fluorouracil and leucovorin as a first-line treatment for metastatic colorectal cancer. A third group of patients was treated with irinotecan alone to determine the activity of this drug as a single agent in a multicenter trial.

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METHODS

Study Design and Entry Criteria

We conducted a phase 3, randomized, open-label, multicenter trial. To be eligible, patients had to have histologically documented colorectal cancer and measurable metastatic disease; an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2; and adequate organ function. Prior therapy for metastatic disease was not permitted; patients who had received adjuvant fluorouracil-based therapy were eligible if they had remained free of disease for at least one year after the completion of adjuvant therapy. Patients who had received pelvic irradiation were excluded. The protocol was approved by the institutional review boards of all participating institutions, and all patients gave written informed consent before enrollment.

Stratification, Randomization, and Therapy

Patients were stratified according to age (<65 years vs. ≥65 years), ECOG performance status (0 vs. 1 or 2), interval from diagnosis to enrollment (<6 months vs. ≥6 months), and history of adjuvant therapy with fluorouracil (yes vs. no) and were then randomly assigned to one of three regimens (Table 1). Treatment was continued until one of the following occurred: disease progression, unacceptable adverse effects, or the withdrawal of consent by the patient. After the first treatment, the doses were adjusted to accommodate individual levels of tolerance. The severity of adverse effects was evaluated with use of the National Cancer Institute Common Toxicity Criteria (version 1.0), in which a grade of 0 indicates no adverse effects, a grade of 1 minor effects, a grade of 2 moderate effects, a grade of 3 severe effects, and a grade of 4 life-threatening effects. The doses of irinotecan and fluorouracil (in the triple-drug group) were reduced by 20 percent during a cycle if a grade 2 adverse effect occurred and were omitted in the event of a grade 3 or 4 effect. Once the adverse effect resolved, treatment was resumed; the dose was reduced by 20 percent in the case of a grade 3 adverse effect and by 40 percent in the case of a grade 4 adverse effect or neutropenic fever. After grade 3 or 4 mucositis, only the doses of fluorouracil were reduced. For the Mayo Clinic bolus regimen, the doses of fluorouracil were reduced by 20 percent after a grade 3 adverse effect and by 40 percent after a grade 4 effect or neutropenic fever.

Supportive care included intensive treatment with loperamide[23] for late diarrhea. Atropine was given as needed for irinotecan-related cholinergic symptoms.[24,25] Antiemetic agents were provided at the discretion of the treating physician. The prophylactic use of colony-stimulating factors was not permitted.

Evaluation of Patients

Tumors were measured every 6 weeks through week 24 and then every 12 weeks until the tumor progressed. An objective response was defined as a reduction of at least 50 percent in the area of all measurable lesions on computed tomographic (CT) or other scanning. Confirmed objective responses were those for which a follow-up scan obtained at least four weeks later demonstrated the persistence of the response. Tumor progression was defined as an increase of at least 25 percent in the overall area of the tumor or the appearance of new lesions. The determination of responses and progression was based on investigator-reported measurements. Safety assessments and complete blood counts were performed weekly. Serum chemical values and the quality of life were assessed at the beginning of each treatment cycle. The Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer (version 2) was used to assess the quality of life. On this test, scores can range from 0 to 100, with higher scores on functional scales and lower scores on symptom scales indicating a better quality of life. Data on subsequent treatments for colorectal cancer and survival were collected approximately every three months after the end of the study treatment.

Statistical Analysis

The primary end point was progression-free survival. Progression-free survival was defined as the length of time from randomization to disease progression or to death from disease progression or unknown causes. For patients who were removed from the study or died of causes unrelated to colorectal cancer, progression-free survival was conservatively defined as the time from randomization to the last date on which the patient was known to be free of progressive disease.

Past experience suggested that the median progression-free survival with fluorouracil and leucovorin would be five months.[4,5] We estimated that 220 patients would be needed in each group in order to detect a 40 percent improvement in median progression-free survival, to seven months, with triple-drug therapy with a power of 0.85.

In the evaluation of efficacy end points, all patients enrolled in the study were included and analyzed according to the intention-to-treat principle. In the analysis of treatment administration and adverse effects, only the patients who actually received treatment were assessed. (Of the 683 patients who enrolled in the study, the 16 who were not treated were excluded from this part of the analysis and the adverse effects in the 4 patients who received the wrong treatment were attributed to the drugs they actually received.) We used two-tailed, unstratified, log-rank tests, with a P value of 0.05 or less considered to indicate statistical significance, in the analyses comparing time-to-event end points between the triple-drug group and the two-drug group, which were selected a priori as the only groups to be used in statistical hypothesis testing. For response rates, we used chi-square tests to compare these two groups. We assessed changes in subscale scores of the quality of life between groups using analysis of variance for repeated meas-

TABLE 1. TREATMENT REGIMENS.*

REGIMEN	STARTING DOSE	SCHEDULE
Irinotecan	125 mg/m² of body-surface area intravenously over a 90-minute period	Each one given weekly for 4 weeks every 6 weeks
Leucovorin	20 mg/m² as an IV bolus	
Fluorouracil	500 mg/m² as an IV bolus	
Leucovorin	20 mg/m² as an IV bolus	Each one given daily for 5 days (on days 1–5) every 4 weeks
Fluorouracil	425 mg/m² as an IV bolus	
Irinotecan alone	125 mg/m² intravenously over a 90-minute period	Given weekly for 4 weeks every 6 weeks

*For each regimen, the agents are listed in the order in which they were administered. IV denotes intravenous.

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ures, whereas we used Student's t-tests to compare the greatest worsening in the quality of life from base line.

We used proportional-hazards modeling with forward selection to determine the influence of the patients' base-line characteristics on response, progression-free survival, and overall survival. A P value of less than 0.05 was considered to indicate statistical significance. Interactions between treatment and the various factors with a P value of less than 0.10 were assessed. Predefined base-line characteristics for this analysis included the four stratification factors and other potentially prognostic factors: sex, race or ethnic group, the site of the primary tumor, the time from diagnosis of disease to the occurrence of metastasis, the number of involved organs, the presence or absence of liver involvement, hemoglobin level, white-cell count, and serum levels of carcinoembryonic antigen, lactate dehydrogenase, and total bilirubin.

RESULTS

Characteristics of the Patients

A total of 683 patients were enrolled in the study and randomly assigned to one of the three treatments between May 1996 and May 1998 at 71 sites in the United States, Canada, Australia, and New Zealand. Data were collected for an additional 19 months after accrual ended, with data on survival collected through December 1999. The intention-to-treat population comprised 231 patients in the group assigned to receive irinotecan, fluorouracil, and leucovorin; 226 patients in the group assigned to receive fluorouracil and leucovorin; and 226 patients in the group assigned to receive irinotecan alone. After the exclusion of the 16 patients who never received therapy and the 4 who received the wrong treatment, the treated population included 225 patients who received irinotecan, fluorouracil, and leucovorin; 219 patients who received fluorouracil and leucovorin; and 223 patients who received irinotecan alone.

Table 2 shows the base-line characteristics of the patients, all of which were balanced among the treatment groups except for the proportion of men, which was greater in the triple-drug group than in the two-drug group (65 percent vs. 54 percent, P=0.02). The median age was just over 60 years. More than 50 percent of the patients had an ECOG performance status of 1 or 2 at base line. Approximately 35 percent of the patients in each group had at least two organs involved, with the liver being the most common site of metastatic disease. Because most patients had metastatic disease at diagnosis, only about 10 percent of them had received adjuvant therapy. In violation of the entry criteria, nine patients had received pelvic radiotherapy. There were no significant differences in base-line laboratory values among the groups.

Treatment

The median duration of treatment with irinotecan, fluorouracil, and leucovorin was 5.5 months. For patients who received fluorouracil and leucovorin and those who received irinotecan alone, the median durations of treatment were 4.1 months and 3.9 months, respectively. The median relative intensity of the dose of irinotecan (calculated as the actual dose delivered divided by the intended dose) was similar in the group given irinotecan alone and the group given irinotecan, fluorouracil, and leucovorin (75 percent vs. 72 percent). The median relative intensity of the dose of fluorouracil in the triple-drug group was lower than that in the two-drug group (71 percent vs. 86 percent). This lower dose intensity may have resulted, in part, from the weekly reductions in dose permitted with the triple-drug regimen.

Among patients with follow-up data, 52 percent of those who received irinotecan, fluorouracil, and leucovorin during the study, 70 percent of those who received fluorouracil and leucovorin, and 79 percent of those who were given irinotecan alone received additional chemotherapy after the study treatment ended. The majority of patients (56 percent) in the group given fluorouracil and leucovorin received an irinotecan-based regimen after the study. Oxaliplatin or other investigational agents were administered to fewer than 5 percent of patients in any group.

Efficacy

Progression-free survival, the primary end point of the study, was significantly longer among patients who were assigned to receive irinotecan, fluorouracil, and leucovorin than among those assigned to receive fluorouracil and leucovorin (median, 7.0 months vs. 4.3 months; P=0.004) (Table 3). Progression-free survival among patients who were assigned to receive irinotecan alone (median, 4.2 months) was similar to that among patients who were assigned to receive fluorouracil and leucovorin. The Kaplan–Meier estimates of progression-free survival in the three groups are shown in Figure 1.

The objective rate of response was 50 percent among patients who were assigned to receive irinotecan, fluorouracil, and leucovorin and 28 percent among those assigned to receive fluorouracil and leucovorin (P<0.001). The rates of objective responses that were confirmed by imaging tests four to six weeks later were also significantly higher among patients in the triple-drug group than among those in the two-drug group (39 percent vs. 21 percent, P<0.001). The rates of objective and confirmed responses with irinotecan alone (29 percent and 18 percent, respectively) were similar to those with fluorouracil and leucovorin (28 percent and 21 percent, respectively). A complete response was seen in six patients in the triple-drug group, two patients in the two-drug group, and four patients assigned to receive irinotecan alone. The median duration of confirmed response was approximately nine months in all groups.

The median survival of patients who were assigned to receive irinotecan, fluorouracil, and leucovorin was 14.8 months, as compared with 12.6 months among patients who were assigned to receive fluorouracil and leucovorin (P=0.04). The median survival of patients

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TABLE 2. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	IRINOTECAN, FLUOROURACIL, AND LEUCOVORIN (N=231)	FLUOROURACIL AND LEUCOVORIN (N=226)	IRINOTECAN ALONE (N=226)
Sex — no. (%)			
Male	151 (65)	123 (54)	145 (64)
Female	79 (34)	101 (45)	80 (35)
Not available†	1 (<1)	2 (1)	1 (<1)
Age‡			
Median — yr	62	61	61
Range — yr	25–85	19–85	30–87
<65 years — no. (%)	139 (60)	136 (60)	135 (60)
≥65 years — no. (%)	91 (39)	88 (39)	90 (40)
Not available — no. (%)†	1 (<1)	2 (1)	1 (<1)
ECOG performance status — no. (%)‡			
0	89 (39)	93 (41)	104 (46)
1	106 (46)	102 (45)	103 (46)
2	35 (15)	29 (13)	18 (8)
Not available†	1 (<1)	2 (1)	1 (<1)
Site of primary tumor — no. (%)			
Colon	188 (81)	192 (85)	189 (84)
Rectum	38 (16)	31 (14)	33 (15)
Not available†	5 (2)	3 (1)	4 (2)
No. of involved organs — no. (%)			
1	147 (64)	149 (66)	140 (62)
2	59 (26)	52 (23)	64 (28)
>2	24 (10)	23 (10)	21 (9)
Not available†	1 (<1)	2 (1)	1 (<1)
Liver involvement — no. (%)			
Yes	189 (82)	185 (82)	188 (83)
No	41 (18)	39 (17)	37 (16)
Not available†	1 (<1)	2 (1)	1 (<1)
Time from diagnosis to randomization — mo‡			
Median	1.9	1.7	1.8
Range	0.1–161	0.1–203	0.1–185
Prior adjuvant fluorouracil — no. (%)‡			
Yes	25 (11)	18 (8)	23 (10)
No	206 (89)	208 (92)	203 (90)
Prior radiotherapy — no. (%)			
Any	7 (3)	5 (2)	3 (1)
Pelvis or abdomen	4 (2)	2 (1)	3 (1)
Other sites	3 (1)	3 (1)	0
Base-line laboratory abnormalities — no./total no. (%)			
White-cell count ≥8×10^3/mm^3	119/227 (52)	115/217 (53)	113/221 (51)
Hemoglobin <11 g/dl	58/227 (26)	55/217 (25)	57/221 (26)
Lactate dehydrogenase > upper normal limit	126/210 (60)	112/201 (56)	104/195 (53)
Total bilirubin > upper normal limit	15/226 (7)	9/218 (4)	22/220 (10)
Carcinoembryonic antigen ≥100 ng/ml	89/224 (40)	82/213 (38)	81/219 (37)

*Because of rounding, percentages may not total 100. ECOG denotes Eastern Cooperative Oncology Group.

†Information was not available for some patients who underwent randomization but were not treated.

‡This was a stratification variable.

assigned to receive irinotecan alone was similar to that of patients assigned to receive fluorouracil and leucovorin (12.0 vs. 12.6 months). The Kaplan–Meier survival curves are shown in Figure 2.

Proportional-Hazards Modeling

Multiple regression modeling of the rates of objective response revealed no interactions between treatment and the stratification factors or other potentially prognostic factors. The addition of irinotecan to therapy with fluorouracil and leucovorin virtually doubled the response rates in all predefined subgroups of patients.

For progression-free and overall survival, we used Cox regression techniques to compare the effects of irinotecan, fluorouracil, and leucovorin with those of fluorouracil and leucovorin in the context of the stratification factors and other predefined base-line clinical characteristics (Table 4). Factors predictive of improved progression-free survival and overall survival were a normal lactate dehydrogenase level and an excellent performance status (a score of 0). A hemo-

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TABLE 3. INTENTION-TO-TREAT ANALYSIS OF EFFICACY.

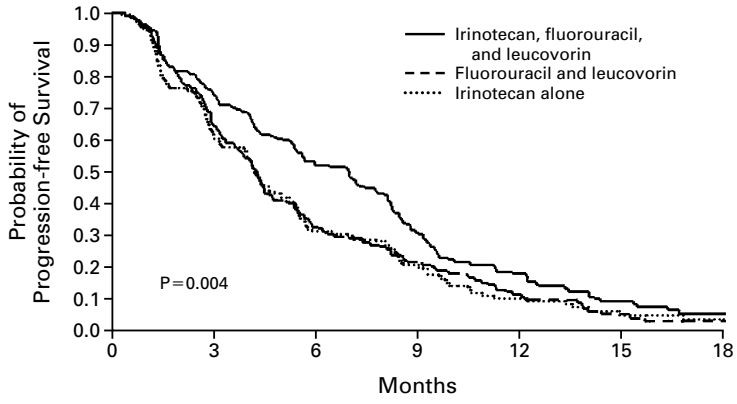
END POINT	IRINOTECAN, FLUOROURACIL, AND LEUCOVORIN (N=231)	FLUOROURACIL AND LEUCOVORIN (N=226)	P VALUE*	IRINOTECAN ALONE (N=226)
Median progression-free survival (mo)	7.0	4.3	0.004†	4.2
Objective response rate (%)	50	28	<0.001‡	29
Confirmed objective response rate (%)§	39	21	<0.001‡	18
Median duration of confirmed response (mo)	9.2	8.7	0.37†	9.0
Median overall survival (mo)	14.8	12.6	0.04†	12.0

*P values are for the comparison of the triple-drug group with the two-drug group.

†The log-rank test was used.

‡The chi-square test was used.

§Responses were confirmed by computed tomography or other scanning four to six weeks after the initial evidence of an objective response had been obtained.



NO. AT RISK							
Irinotecan, fluorouracil, and leucovorin	231	154	99	49	23	11	5
Fluorouracil and leucovorin	226	124	54	32	15	5	2
Irinotecan alone	226	112	51	29	12	4	1

Figure 1. Kaplan–Meier Estimates of Progression-free Survival.
The P value was derived from a log-rank test comparing the triple-drug group with the two-drug group.

globin level of at least 11 g per deciliter and a normal white-cell count were predictive of better progression-free survival and overall survival, respectively. Unexpectedly, an age of 65 years or older was also associated with a longer progression-free survival. Treatment with irinotecan, fluorouracil, and leucovorin remained a significant independent predictor of longer progression-free survival ($P<0.001$) and overall survival ($P=0.03$) when other significant base-line characteristics were taken into account. Treatment with irinotecan, fluorouracil, and leucovorin was associated with a 36 percent reduction in the risk of progression and a 22 percent reduction in the risk of death relative to treatment with fluorouracil and leucovorin alone (Table 4). No relevant interactions between treatment and other factors were identified for progression-free survival, indicating that progression-free survival was improved in all the predefined subgroups of patients. In the comparison of irinotecan, fluorouracil, and leucovorin with fluorouracil and leucovorin, the reduction in the risk of death among patients with a normal lactate dehydrogenase level was 43 percent, as compared with a reduction of 12 percent among those with an elevated lactate dehydrogenase level,

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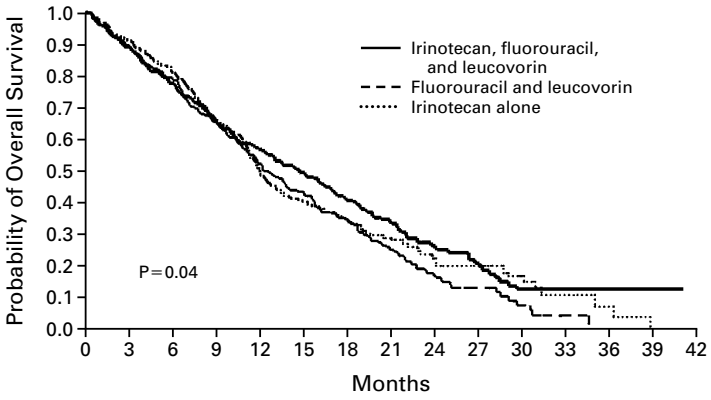

No. at Risk								
Irinotecan, fluorouracil, and leucovorin	231	178	129	84	33	10	3	1
Fluorouracil and leucovorin	226	175	116	72	23	5	0	0
Irinotecan alone	226	181	110	69	28	11	2	0

Figure 2. Kaplan–Meier Estimates of Overall Survival.
The P value was derived from a log-rank test comparing the triple-drug group with the two-drug group.

Table 4. Results of Cox Regression Analysis.*

Factor	Progression-free Survival		Overall Survival	
	Hazard Ratio (95% CI)	P value	Hazard Ratio (95% CI)	P value
Serum lactate dehydrogenase (≤UNL vs. >UNL)	0.60 (0.47–0.76)	<0.001	0.47 (0.36–0.60)	<0.001
No. of involved organs (1 vs. ≥2)	0.63 (0.50–0.80)	<0.001	0.67 (0.54–0.83)	<0.001
Performance status (0 vs. 1 or 2)	0.74 (0.59–0.93)	0.009	0.56 (0.44–0.70)	<0.001
Bilirubin level (≤UNL vs. >UNL)	0.56 (0.35–0.89)	0.01	0.53 (0.33–0.83)	0.005
White-cell count (<8×10^3/mm^3 vs. ≥8×10^3/mm^3)†	—	—	0.65 (0.52–0.82)	<0.001
Hemoglobin level (≥11 g/dl vs. <11 g/dl)‡	0.74 (0.58–0.95)	0.02	—	—
Age (≥65 yr vs. <65 yr)	0.78 (0.63–0.98)	0.03	0.82 (0.65–1.02)	0.08§
Treatment (irinotecan, fluorouracil, and leucovorin vs. fluorouracil and leucovorin)	0.64 (0.51–0.79)	<0.001	0.78 (0.63–0.97)	0.03

*CI denotes confidence interval, and UNL upper limit of normal.

†This variable was not included in the analysis of progression-free survival, because it was not significant.

‡This variable was not included in the analysis of overall survival, because it was not significant.

§Age was identified as a stratification factor in the study design and was therefore included in the model even though it was only marginally significant (P=0.08).

suggesting a possible interaction of the lactate dehydrogenase level with treatment with respect to survival (P=0.07).

Adverse Effects

As shown in Table 5, 22.7 percent of patients who were given irinotecan, fluorouracil, and leucovorin had diarrhea of grade 3 or 4, as compared with 13.2 percent of patients who were given fluorouracil and leucovorin and 31.0 percent of patients who were given irinotecan alone. The difference between the triple-drug group and the two-drug group was primarily in the incidence of grade 3 diarrhea; the incidence of grade 4 diarrhea was similar in the two groups (7.6

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percent and 7.3 percent). The group given irinotecan alone had an incidence of grade 4 diarrhea of 12.6 percent. Vomiting of grade 3 or 4 was more common with combination regimens that included irinotecan. Mucositis of grade 3 or 4 occurred in only 2.2 percent of patients who received irinotecan alone or in combination. As expected, the Mayo Clinic bolus regimen of fluorouracil and leucovorin was associated with a much higher frequency of grade 3 or 4 mucositis (16.9 percent). Moreover, the frequency of grade 4 neutropenia during treatment with irinotecan, fluorouracil, and leucovorin was almost half that observed during treatment with fluorouracil and leucovorin (24.0 percent vs. 42.5 percent); neutropenic fever was also less common with irinotecan, fluorouracil, and leucovorin than with fluorouracil and leucovorin (7.1 percent vs. 14.6 percent). Irinotecan alone was associated with the lowest incidence of grade 3 or 4 neutropenia. The incidence of treatment-related death was approximately 1 percent in all three groups.

Table 5. Adverse Events among Patients Who Received the Assigned Treatment.*

Adverse Event	Irinotecan, Fluorouracil, and Leucovorin (N=225)	Fluorouracil and Leucovorin (N=219)	Irinotecan Alone (N=223)
		percent	
Diarrhea			
Grade 3 or 4	22.7	13.2	31.0
Grade 3	15.1	5.9	18.4
Grade 4	7.6	7.3	12.6
Vomiting			
Grade 3 or 4	9.7	4.1	12.1
Grade 3	5.3	2.7	5.8
Grade 4	4.4	1.4	6.3
Mucositis			
Grade 3 or 4	2.2	16.9	2.2
Grade 3	2.2	14.6	1.8
Grade 4	0	2.3	0.4
Neutropenia			
Grade 3 or 4	53.8	66.2	31.4
Grade 3	29.8	23.7	19.3
Grade 4	24.0	42.5	12.1
Neutropenic complications			
Fever	7.1	14.6	5.8
Infection	1.8	0.0	2.2
Discontinuation related to adverse events	7.6	6.4	11.7
Drug-related deaths	0.9	1.4	0.9

*A grade of 3 indicated a severe event, and a grade of 4 a life-threatening event.

Quality of Life

Analyses of the quality of life showed that there were no significant differences between the group given irinotecan, fluorouracil, and leucovorin and the group given fluorouracil and leucovorin (Fig. 3). In univariate analyses in which we compared the greatest worsening in the quality of life from base line, the mean increases in the severity of symptoms were smaller in the triple-drug group than in the two-drug group with respect to fatigue (increase in severity, 8 percent vs. 20 percent), anorexia (1 percent decrease vs. 9 percent increase), and pain (increase, 1 percent vs. 8 percent) ($P<0.05$ for all comparisons, by Student's t-test). As indicated by the measurement of the greatest declines from base line in role functioning (the ability to perform the activities of daily living), the triple-drug group had a smaller decrease in function than the two-drug group (decrease, 6 percent vs. 13 percent; $P<0.05$ by Student's t-test). The extent of the changes in other subscales in this analysis was not significantly different between the groups.

DISCUSSION

In this phase 3, randomized study, we compared the clinical benefits of a combination of irinotecan plus fluorouracil and leucovorin with those of fluorouracil and leucovorin alone as first-line therapy for metastatic colorectal cancer. The control regimen of fluorouracil and leucovorin that we used has been one of the most commonly used treatments for metastatic colorectal cancer in North America; thus, our findings can give practitioners insight into the relative efficacy and safety of the new regimen as contrasted with a familiar standard.

The base-line clinical characteristics of the treatment groups were similar except for a greater proportion of men in the group assigned to receive irinotecan, fluorouracil, and leucovorin than in the group assigned to receive fluorouracil and leucovorin. However, this difference did not appear to influence the results; when sex was tested in multivariate analyses, it was not significantly predictive of the outcome.

Our results show that, as compared with fluorouracil-based therapy, the combination of irinotecan, fluorouracil, and leucovorin significantly delays disease progression while reducing the size of tumors. Progression-free survival was significantly longer among patients who were assigned to receive irinotecan, fluorouracil, and leucovorin than among those assigned to receive fluorouracil and leucovorin (median progression-free survival, 7.0 and 4.3 months, respectively; $P=0.004$), with an average reduction of 36 percent in the risk of disease progression at any given time. The rates of response with irinotecan, fluorouracil, and leucovorin were close to double those with fluorouracil and leucovorin (50 percent vs. 28 percent, $P<0.001$). Improvements in response rates and progression-free survival were observed in every subgroup of patients in the triple-drug group, including those with a poor ECOG performance status, an age of 65 years or older, extensive disease, a history of adjuvant therapy, or abnormal laboratory values at base line.

Treatment with irinotecan, fluorouracil, and leucovorin was also associated with a statistically signif-

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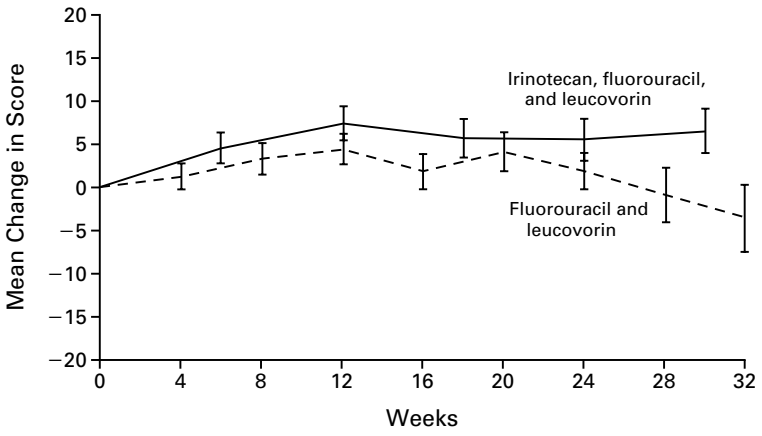

No. at Risk									
Irinotecan, fluorouracil, and leucovorin	222	166	145	125	107	87			
Fluorouracil and leucovorin	218	167	152	131	109	84	71	54	48

Figure 3. Mean (±SE) Changes from Base Line in Scores on the Global Health Status Subscale of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer.

On this scale, scores can range from 0 to 100, with higher scores indicating a better quality of life.

icant improvement in overall survival (median, 14.8 months, as compared with 12.6 months in the group assigned to fluorouracil and leucovorin; $P=0.04$). Evaluation of the hazard ratio for the three-drug group relative to the two-drug group indicated that, at any given time, the relative risk of death in the triple-drug group was an average of 22 percent lower. The improvement in survival in the patients who received the triple-drug combination is particularly notable because over half the patients in the control group eventually received irinotecan as second-line therapy. Thus, concurrent first-line administration of irinotecan and fluorouracil appears to be superior to sequential administration.

We performed a Cox regression analysis of prognostic factors identified in other trials[19,20,26-28] and confirmed that a good performance status, fewer metastatic sites, relatively normal laboratory results (normal lactate dehydrogenase and bilirubin levels, normal white-cell count, and a hemoglobin level of at least 11 g per deciliter) are associated with better outcomes. After adjustment for these factors, the difference between the group given irinotecan, fluorouracil, and leucovorin and the group given fluorouracil and leucovorin remained significant with respect to improvements in both progression-free survival ($P<0.001$) and overall survival ($P=0.03$).

As stipulated by the protocol, the irinotecan-alone group was not the focus of statistical testing. However, as expected, the efficacy results in this group were generally consistent with those observed with fluorouracil and leucovorin alone.

The results of our study complement the findings of another phase 3 trial comparing irinotecan, fluorouracil, and leucovorin with fluorouracil and leucovorin as first-line therapy for metastatic colorectal cancer.[29] That study, conducted primarily in Europe, randomly assigned 385 patients to receive either irinotecan plus infusions of fluorouracil and leucovorin or infusions of fluorouracil and leucovorin alone. The results of both studies are remarkably consistent; in the European trial, progression-free survival was significantly improved with the triple-drug therapy as compared with the two-drug therapy (median, 6.7 months vs. 4.4 months; $P<0.001$). Likewise, the confirmed objective response rate in the group given irinotecan, fluorouracil, and leucovorin was significantly higher than the rate in the group given fluorouracil and leucovorin (35 percent vs. 22 percent, $P<0.005$). The addition of irinotecan resulted in an improvement in survival of approximately 20 percent (median, 17.4 months vs. 14.1 months; $P=0.03$), results that were similar to those in our study.

In our study, the incidence of grade 3 diarrhea was greater with triple-drug therapy than with two-drug therapy. However, grade 4 diarrhea — largely defined by the need for hospitalization for supportive care — was infrequent (<8 percent) in both groups. The incidence of grade 4 diarrhea was lower with irinotecan, fluorouracil, and leucovorin than with irinotecan alone, perhaps because the neutropenia induced by fluorouracil and leucovorin in the three-drug group prompted early midcycle reductions in the dose of irinotecan and fluorouracil that lowered the risk of grade 4 diarrhea.

Vomiting of grade 3 or 4 was more common with

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irinotecan, fluorouracil, and leucovorin than with fluorouracil and leucovorin, but it occurred in less than 10 percent of patients in the three-drug group, and its incidence might have been further reduced with the more frequent use of prophylactic serotonin-antagonist antiemetics. Mucositis of grade 3 or 4, grade 4 neutropenia, and neutropenic fever occurred less often with triple-drug therapy than with two-drug therapy. This finding most likely results from differences in the scheduling of fluorouracil and leucovorin treatments in the two regimens; the combination of fluorouracil and leucovorin is associated with lower rates of these adverse effects when it is given weekly.[4,5] Treatment-related death was rare (a rate of 1 percent in all groups). Furthermore, analysis of the quality of life indicated that the combination of irinotecan with fluorouracil and leucovorin did not worsen the quality of life as compared with that reported with fluorouracil and leucovorin.

In conclusion, we found that combining irinotecan with fluorouracil and leucovorin benefits patients with metastatic colorectal cancer. As compared with a widely used regimen of fluorouracil and leucovorin, the triple-drug therapy was associated with higher rates of tumor regression, progression-free survival, and overall survival without compromising the quality of life. The combination of irinotecan, fluorouracil, and leucovorin is now being compared with a weekly regimen of fluorouracil and leucovorin as adjuvant therapy for patients with stage III colon cancer to determine whether it will increase rates of cure in patients with an earlier stage of the disease.

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APPENDIX

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