VOLUME 22 · NUMBER 1 · JANUARY 1 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

A Randomized Controlled Trial of Fluorouracil Plus Leucovorin, Irinotecan, and Oxaliplatin Combinations in Patients With Previously Untreated Metastatic Colorectal Cancer

Richard M. Goldberg, Daniel J. Sargent, Roscoe F. Morton, Charles S. Fuchs, Ramesh K. Ramanathan, Stephen K. Williamson, Brian P. Findlay, Henry C. Pitot, and Steven R. Alberts

From the North Central Cancer Treatment Group, Divisions of Hematology/Oncology and Medical Oncology, University of North Carolina at Chapel Hill, Chapel Hill, NC; North Central Cancer Treatment Group, Division of Biostatistics, Mayo Clinic, Rochester, MN; North Central Cancer Treatment Group, Iowa Oncology Research Association Community Clinical Oncology Program, Des Moines, IA; Cancer and Acute Leukemia Group B, Department of Oncology, Dana-Farber Cancer Institute, Boston, MA; Eastern Cooperative Oncology Group, Division of Medical Oncology, University of Pittsburgh Cancer Institute, Pittsburgh, PA; Southwestern Oncology Group, Division of Hematology and Oncology, University of Kansas Medical Center, Kansas City, KS; National Cancer Institute of Canada, St Catharines, Ontario, Canada.

Submitted September 9, 2003; accepted October 3, 2003.

Supported by National Institutes of Health grants CA25224, CA32102, CA38926, CA21115, and CA77202, Pharmacia Corp, and Sanofi-Synthelabo. Pharmacia and Sanofi-Synthelabo provided irinotecan and oxaliplatin, respectively, for this study, and both approved the study protocol.

Presented in part at the 2001 (May 12-15, 2001, San Francisco, CA), 2002 (May 18-21, 2002, Orlando, FL), and 2003 (May 31-June 3, 2003, Chicago, IL) Annual Meetings of the American Society of Clinical Oncology.

Nothing in this article implies endorsement of the products of Pharmacia (Pfizer) Corp or Sanofi-Synthelabo.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Richard M. Goldberg, MD, Division of Hematology/Oncology, University of North Carolina at Chapel Hill, CB#7305, 3009 Old Clinic Building, Chapel Hill, NC 27599-7305; e-mail: goldberg@med.unc.edu.

0732-183X/04/2201-23/$20.00

DOI: 10.1200/JCO.2004.09.046

ABSTRACT

Purpose
Three agents with differing mechanisms of action are available for treatment of advanced colorectal cancer: fluorouracil, irinotecan, and oxaliplatin. In this study, we compared the activity and toxicity of three different two-drug combinations in patients with metastatic colorectal cancer who had not been treated previously for advanced disease.

Patients and Methods
Patients were concurrently randomly assigned to receive irinotecan and bolus fluorouracil plus leucovorin (IFL, control combination), oxaliplatin and infused fluorouracil plus leucovorin (FOLFOX), or irinotecan and oxaliplatin (IROX). The primary end point was time to progression, with secondary end points of response rate, survival time, and toxicity.

Results
A total of 795 patients were randomly assigned between May 1999 and April 2001. A median time to progression of 8.7 months, response rate of 45%, and median survival time of 19.5 months were observed for FOLFOX. These results were significantly superior to those observed for IFL for all end points (6.9 months, 31%, and 15.0 months, respectively) or for IROX (6.5 months, 35%, and 17.4 months, respectively) for time to progression and response. The FOLFOX regimen had significantly lower rates of severe nausea, vomiting, diarrhea, febrile neutropenia, and dehydration. Sensory neuropathy and neutropenia were more common with the regimens containing oxaliplatin.

Conclusion
The FOLFOX regimen of oxaliplatin and infused fluorouracil plus leucovorin was active and comparatively safe. It should be considered as a standard therapy for patients with advanced colorectal cancer.

J Clin Oncol 22:23-30. © 2004 by American Society of Clinical Oncology

INTRODUCTION

In 2002, approximately 150,000 people in the United States were newly diagnosed with colorectal cancer, a disease that ranks as the third leading cause of cancer death worldwide [1]. For years, effective treatment for advanced colorectal cancer was limited to fluorouracil (FU). There are preclinical in vitro, as well as clinical in vivo, data that suggest that FU has a schedule-dependent mechanism of action [2]. When the agent is delivered by a short-duration bolus injection, it mainly inhibits RNA synthesis. When FU is delivered by long-term infusion lasting days to weeks, it mainly inhibits DNA synthesis through inhibition of thymidylate synthesis. Historically, treatment with bolus FU led to modest response rates of approximately 12%, and a median survival of approximately 11 months.

Delivering FU by infusion of 24-hour or longer durations changes the toxicity profile and seems to improve the response rate, while prolonging median survival modestly by less than a month, from 11 to 12 months. The coupling of FU with leucovorin (LV), a reduced folate that increases thymidylate

synthetase inhibition, improves clinical outcomes [3]. Like the differences observed with FU alone, the activity and toxicity of FU plus LV (FU/LV) depends on administration of FU via bolus injection or infusion. Before 2000, regimens based on the bolus injection of FU/LV were the North American standard treatment for advanced colorectal cancer. A 1,381-patient meta-analysis indicated a response rate of 23%, and a median survival of 11.5 months [3].

In Europe, it is more common to administer FU as a short-term infusion. For example, a group of French physicians led by Aimery de Gramont developed a regimen repeated every other week that employed a schedule of two consecutive daily 2-hour LV infusions, followed by bolus injections of FU, followed by 22-hour infusions of FU. A randomized comparison of this regimen, designated LVFU-2, with the Mayo Clinic 5-consecutive-day program of FU/LV demonstrated a response rate of 37% *v* 14%, and a median survival of 14.3 months versus 13.1 months [4].

In the 1990s, two additional agents, irinotecan and oxaliplatin, were found to have activity against advanced colorectal cancer. Irinotecan inhibits topoisomerase I, thus impeding DNA uncoiling leading to double-stranded DNA breaks [5]. Initial treatment with irinotecan and either bolus (North American preference) or infused (European preference) FU/LV significantly improved outcomes as compared with FU/LV [6,7]. The bolus regimen of irinotecan plus FU/LV, commonly known as IFL, produced a 39% response rate, 7-month median time to progression, and median overall survival of 14.8 months [6]. In March 2000, the US Food and Drug Administration approved this combination as indicated for first-line therapy for advanced colorectal cancer. The Oncologic Drugs Advisory Committee recommended to the US Food and Drug Administration that this combination be considered a regulatory standard to which new regimens be compared. A second trial done in Europe added irinotecan to bolus and infused FU/LV, with results comparable to those observed with IFL [7].

Oxaliplatin, a platinum-based drug, forms cross-linking adducts, thus blocking DNA replication and transcription [8]. In vitro oxaliplatin inhibits colorectal tumor cell lines resistant to cisplatin and carboplatin [9]. When the infused LVFU-2 regimen described earlier was compared with a regimen of oxaliplatin plus LVFU-2 known as FOLFOX4, the latter treatment significantly increased the response rate to 51%, and the time to progression to 9.0 months. The increase in median survival from 14.7 to 16.2 months did not reach statistical significance [10].

Preliminary phase I/II trials indicated activity for an every-3-week oxaliplatin and irinotecan (IROX) regimen that was similar to that noted previously for IFL [11,12]. Our study is the first phase III trial to evaluate oxaliplatin and irinotecan in combination.

We developed this randomized multicenter trial to compare combinations of FU/LV, irinotecan, and oxaliplatin in patients with previously untreated metastatic colorectal cancer. Several early changes in the study that do not materially affect the results presented here, and that will be reported in a separate publication, are cataloged here for the sake of completeness (Fig 1). These changes included dele-

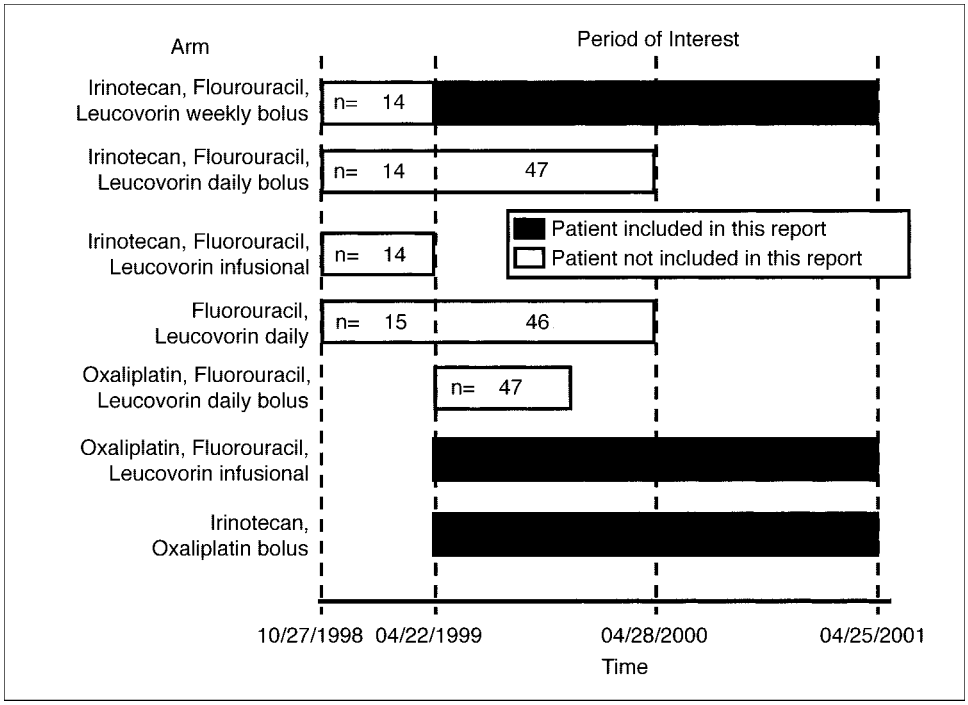

Fig 1. Timeline.

tion of three treatment arms, all using bolus FU/LV for toxicity; the addition of three oxaliplatin-containing regimens; and replacement of FU/LV with irinotecan and FU/LV as the control regimen [13]. The investigators, in collaboration with the North Central Cancer Treatment Group External Data Monitoring Committee, implemented these changes, which were not based on efficacy considerations. In April 2000, the trial had three arms: the control regimen of IFL compared with two experimental regimens, oxaliplatin and infused FU/LV (FOLFOX) and IROX, and the experience with these three regimens is the subject of this report.

In April 2001, we detected an imbalance (by arm) in the number of deaths within the first 60 days of treatment, with a higher number of deaths in the IFL control arm [14]. Consequently, on the recommendation of the External Data Monitoring Committee, doses of irinotecan and FU were reduced in that arm. Herein we report the comparative efficacy and toxicity data for 795 patients concurrently randomized to the full-dose IFL control regimen or to one of the experimental regimens, FOLFOX or IROX.

PATIENTS AND METHODS

Five National Cancer Institute cooperative oncology groups collaborated in this study: North Central Cancer Treatment Group (lead group), Cancer and Acute Leukemia Group B, Eastern Cooperative Oncology Group, Southwestern Oncology Group, and the National Cancer Institute of Canada. Inclusion and exclusion criteria are enumerated in Table 1.

Patient Evaluation

Physical examination and laboratory studies, including CBC with differential, serum liver function tests, prothrombin time (if receiving warfarin), actual or estimated creatinine clearance, and electrocardiography were performed within 14 days of enrollment. Chest radiography and disease site imaging were completed within 30 days of enrollment. Women of childbearing potential had a negative serum pregnancy testing within 7 days of registration.

CBCs with differential were monitored weekly. Medical history, physical examination, and laboratory evaluation occurred before each cycle. Tumors were measured every 6 weeks for the first 42 weeks or until tumor response was confirmed. Measurements thereafter were required every 12 weeks.

Random Assignment and Stratification

Patients were randomly assigned to treatment through dynamic allocation designed to balance random assignment for the following factors: performance status score (0, ½), prior adjuvant chemotherapy (yes or no), prior immunotherapy (yes or no), age ($<$ 65 years or $\geq$ 65 years), and randomizing location. This protocol was scrutinized and approved by the institutional review board of each participating institution. Each patient provided written informed consent.

Response and Progression Criteria

Study enrollment required either at least one measurable lesion ($\geq$ 2 cm in diameter) or disease that could be serially evaluated to establish whether the disease was getting better or worse (assessable disease). Complete response required that all disease disappear without new lesions. Partial response required at least a 50% reduction in the sum of the products of the longest perpendicular diameters of all measurable lesions. Regression required documented tumor reduction in assessable patients who did not have disease that met the guidelines for measurable disease. Disease progression required 25% or greater increase in measurable tumor or an increase in tumor size in patients whose lesions did not meet the criteria for measurable disease. After partial response, tumor measurements exceeding 50% of the maximal extent of a previously observed reduction constituted progression. Any new lesion constituted progression. Patients who did not meet the definitions of response or progression were classified as having stable disease.

Time to progression was calculated from study entry to disease progression, regardless of the patient's treatment status. In a

Table 1. Eligibility Criteria

Inclusion Criteria	Exclusion Criteria
Histologically proven unresectable colorectal adenocarcinoma	Adjuvant fluorouracil in previous 12 months
Biopsy required if Dukes' A or B primary or $\geq$ 5 years since surgery	Prior treatment for advanced disease
Age $\geq$ 18 years	Prior radiation to $\geq$ 15% of bone marrow
Life expectancy $>$ 12 weeks	Radiotherapy or major surgery within 4 weeks
Eastern Cooperative Oncology Group performance status $\leq$ 2	Minor surgery within 2 weeks
Effective contraception if of childbearing potential	Uncontrolled infection
Neutrophils $\geq 1.5 \times 10^9$/L	Symptomatic peripheral neuropathy
Platelets $\geq 100 \times 10^9$/L	Known brain or meningeal metastases
Hemoglobin $\geq$ 9.0 g/dL	Interstitial pneumonia
Creatinine, total bilirubin $\leq$ 1.5 $\times$ institutional upper normal limit	Grade $\geq$ 2 dyspnea
Aspartate aminotransferase, alkaline phosphatase $\leq$ 5 $\times$ institutional upper normal limit	$\geq$ 3 loose stools per day
Signed informed consent	Comorbid condition that could confound outcome
Institutional review board approval	Pregnancy or lactation
	Active or prior malignancy in the past 3 years (exceptions: nonmelanoma skin cancer, cervical carcinoma in situ, other malignancy with $<$ 10% chance of relapse within 3 years)

post hoc sensitivity analysis, patients were censored for time to progression when they discontinued initial treatment. Deaths occurring within 30 days of treatment discontinuation were considered progressions in both analyses. Survival was calculated from enrollment to death or last contact. Without contradictory data, patients who died or were lost to follow-up were assumed to have progressed at the time they were last documented to be progression-free.

Treatment Plan

The regimens (doses in mg/m^2) were as follows: IFL was irinotecan 125 and bolus FU 500 plus LV 20 on days 1, 8, 15, and 22 every 6 weeks; FOLFOX was oxaliplatin 85 on day 1 and bolus FU 400 plus LV 200 followed by FU 600 in 22-hour infusions on days 1 and 2 every 2 weeks; and IROX was oxaliplatin 85 and irinotecan 200 every 3 weeks. Treatment continued until progression, unmanageable toxic effects, or withdrawal of consent.

Toxic effects (except paresthesias) were graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Functional impairments that interfered with daily activities or caused disability were classified as grade 3 or 4 paresthesias, respectively. Any grade 3 or 4 toxic effect resulted in an approximately 20% dose reduction for subsequent cycles. Persistent grade 2 or worse toxic effects delayed therapy until toxicity resolved. If the toxic effect exceeded grade 1 after 2 weeks or if more than two dose reductions were required, protocol therapy was discontinued.

Statistical Considerations

The primary objective was time to progression, comparing the control regimen with the experimental regimens. The protocol-specified enrollment of 375 patients per arm afforded 90% power to detect a hazard ratio of 0.75 between each experimental regimen and control, using a two-sided log-rank test at level 0.025 for each comparison, maintaining the overall type I error rate at 0.05. An interim analysis using O'Brien-Fleming boundaries after 50% of patients progressed was planned [15]. There were 795 patients enrolled before the dose reductions of irinotecan and FU. Based on that sample size, the recalculated power was 80% to detect a hazard ratio of 0.75.

The main secondary end point of interest was overall survival. Additional secondary end points included confirmed tumor response rate (complete response, partial response in measurable patients, or regression in evaluable patients, confirmed at second evaluation), time to treatment discontinuation (time from random assignment to treatment cessation on assigned treatment), and toxicity.

The Kaplan-Meier method was used to describe the distribution of time to disease progression, overall survival time, and time to treatment discontinuation [16]. Cox proportional hazards modeling was used to calculate hazard ratios and CIs [17]. χ^2 Tests were used to compare toxicity and confirmed response rates. *P* values less than .025 were considered statistically significant for the primary comparison of time to progression between the control and experimental arms; for all other comparisons, *P* values less

Table 2. Baseline Patient Characteristics

Variable	Irinotecan and Fluorouracil Plus Leucovorin (control; n = 264)		Oxaliplatin and Fluorouracil Plus Leucovorin (n = 267)		Oxaliplatin and Irinotecan (n = 264)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years						
Median	61		61		61	
Range	28–88		27-88		29-84	
Disease status						
Measurable	222	84	215	80	219	83
Evaluable	36	14	47	18	38	14
Unknown	6	2	5	2	7	3
ECOG PS						
0-1	246	93	247	93	244	92
2	12	5	15	5	13	5
Unknown	6	2	5	2	7	3
Sex						
Female	92	35	110	41	103	39
Male	172	65	157	59	161	61
Prior adjuvant chemotherapy						
Yes	38	15	42	16	40	15
No	220	83	220	82	217	82
Unknown	6	2	5	2	7	3
Race						
White	226	86	238	89	237	90
Black	26	10	13	5	17	6
Other	12	4	16	6	10	4

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

than .05 were considered statistically significant. All randomized patients are included for efficacy analyses according to intention-to-treat principles; patients who canceled before the initiation of therapy were excluded from toxicity analyses.

RESULTS

Patient Characteristics

There were 795 patients enrolled between May 1999 and April 2001. The arms were well-balanced with respect to stratification factors and other baseline characteristics (Table 2). Twenty-one patients (2.6%) were deemed ineligible, had major treatment violations, or canceled treatment.

Efficacy

With a median follow-up of 20.4 months, 85% of patients had disease progression. Time to disease progression differed significantly between patients receiving IFL (median, 6.9 months) and those receiving FOLFOX (median, 8.7 months; $P = .0014$; hazard ratio, 0.74; 95% CI, 0.61 to 0.89; Fig 2A). In the sensitivity analysis, in which patients whose initial treatment ceased without progression were censored, these results remained significant (median time to disease progression, 7.0 and 9.3 months, respectively; $P = .0015$). The median time to tumor progression was 6.5 months for patients receiving IROX, which was no different than those receiving IFL ($P > .50$; hazard ratio, 1.02; 95% CI, 0.85 to 1.23). The time to progression for patients receiving FOLFOX significantly exceeded that for those receiving IROX ($P = .001$; hazard ratio, 0.72; 95% CI, 0.60 to 0.87).

The median survival for patients receiving IFL was 15.0 months compared with 19.5 months for those receiving FOLFOX ($P = .0001$; hazard ratio, 0.66; 95% CI, 0.54 to 0.82) and 17.4 months for those receiving IROX ($P = .04$ for comparison with IFL; hazard ratio, 0.81; 95% CI, 0.66 to 1.00). Survival for patients receiving FOLFOX did not differ from those receiving IROX ($P = .09$; hazard ratio, 0.83; 95% CI, 0.67 to 1.03; Fig 2B). The response rate of patients receiving FOLFOX (45%) was higher than for those receiving IFL (31%, $P = .002$) or IROX (35%, $P = .03$). The response rates of patients receiving IFL and IROX did not differ ($P = .34$).

Time to treatment discontinuation did not differ significantly for any pairwise comparison (Fig 2C). The reason for treatment discontinuation did differ between arms. Among patients receiving IFL, 67% ceased treatment because of disease progression or death, compared with 42% of patients receiving FOLFOX ($P < .0001$) and 55% receiving IROX ($P = .004$). In this study, only two dose reductions for toxicity were permitted. If a patient continued to have substantial toxicity after two dose reductions, they were removed from the study and treated at the investigator's discretion. In the two arms containing oxaliplatin, patients who went off the study because of toxicity did so most commonly for neutropenia or for paresthesias.

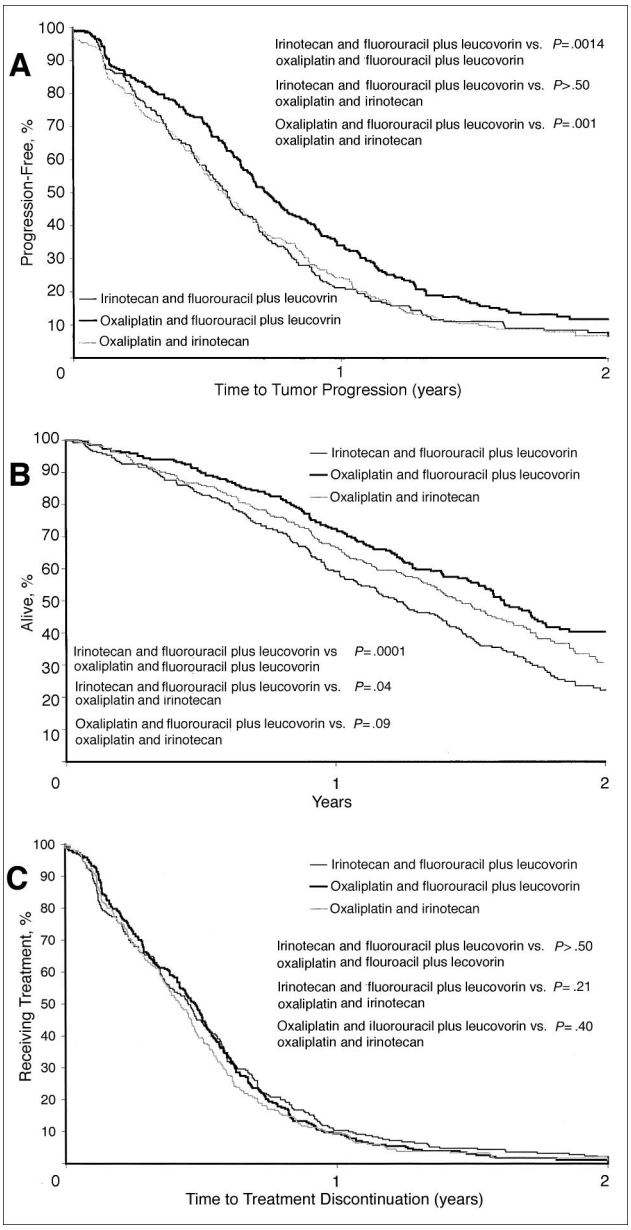

Fig 2. (A) Time to tumor progression. (B) Overall survival. (C) Time to treatment discontinuation.

Adverse Events

The rates of grade 3 or higher toxicity are presented in Table 3. Patients treated with IFL had significantly higher rates of diarrhea, vomiting, nausea, febrile neutropenia, and dehydration, and significantly lower rates of paresthesias and neutropenia compared with patients treated with FOLFOX. The onset of grade 3 paresthesias in patients receiving FOLFOX occurred after a median of twelve 2-week treatment cycles. The rates of grade 3 or higher toxicity for patients receiving IROX were similar to those for patients receiving IFL.

Table 3. Toxicity Grade ≥ 3 and Second-Line Treatment

Toxicity Grade ≥3	Irinotecan and Fluorouracil Plus Leucovorin (n = 255)	Oxaliplatin and Fluorouracil Plus Leucovorin (n = 258)	P*	Oxaliplatin and Irinotecan (n = 256)	P†	P‡
Nausea	16	6	.001	19	.43	.001
Vomiting	14	3	.001	22	.02	.001
Diarrhea	28	12	.001	24	.35	.001
Febrile neutropenia	15	4	.001	11	.23	.002
Dehydration	9	4	.03	6	.17	.41
Paresthesias	3	18	.001	7	.04	.001
Neutropenia	40	50	.04	36	.35	.002

NOTE. Values are percentages of patients in each treatment group.
*Irinotecan and fluorouracil plus leucovorin compared with oxaliplatin and fluorouracil plus leucovorin.
†Irinotecan and fluorouracil plus leucovorin compared with oxaliplatin plus irinotecan.
‡Oxaliplatin and fluorouracil plus leucovorin compared with oxaliplatin plus irinotecan.

The death rates within the first 60 days of treatment were 4.5% (95% CI, 2.4% to 7.8%) for patients receiving IFL, 2.6% (95% CI, 1.1% to 5.3%) for those receiving FOLFOX, and 2.7% (95% CI, 1.1% to 5.4%) for those receiving IROX.

Second-Line Therapy

Treatments administered after first-line therapy are shown in Table 4. We mandated that therapies administered after progression on protocol therapy be reported, but second-line treatments were not specified by the protocol. The proportion of patients receiving any second-line therapy before progression was similar across arms at 26% to 32%. A high proportion (60%) of patients treated with FOLFOX received second-line irinotecan. Fewer patients (24%) receiving IFL were treated with oxaliplatin regimens as second-line therapy, largely owing to the limited availability of that agent during the time that this study was underway.

DISCUSSION

This study provides convincing evidence that FOLFOX is an active regimen for treatment of patients with previously untreated advanced colorectal cancer, extending observations made by other investigators from smaller phase III trials. Treatment with this regimen led to a statistically significantly improved response rate and time to disease progression, confirming prior reports [10,18]. A finding unique to this trial was the statistically significant advantage in overall survival for FOLFOX compared with the control regimen of IFL. Patients treated with FOLFOX experienced the longest median survival (19.5 months) reported to date in a North American phase III trial in patients with advanced colorectal cancer.

Additionally, the adverse event profile for FOLFOX was favorable in comparison with either IFL or IROX. Ox-

Table 4. Second-Line Therapy

Second-Line Therapy	% of Patients		
	Irinotecan and Fluorouracil Plus Leucovorin (n = 251)	Oxaliplatin and Fluorouracil Plus Leucovorin (n = 259)	Oxaliplatin and Irinotecan (n = 262)
Any			
Overall	67	75	70
Before progression	32	26	26
Irinotecan			
Overall	25	60	32
Before progression	9	25	10
Oxaliplatin			
Overall	24	8	9
Before progression	17	3	3
Fluorouracil			
Overall	41	40	50
Before progression	18	14	21

aliplatin may cause sensory neuropathy, an adverse effect that is cumulative but generally reversible and dose-dependent. This tended to become treatment-limiting only in patients benefiting from treatment, as it generally occurred after eight to ten cycles. FOLFOX was also associated with treatment-limiting neutropenia, but this was seldom complicated by clinically meaningful toxicity such as infections. The significantly lower rates of nausea, vomiting, diarrhea, dehydration, and febrile neutropenia associated with this regimen as compared with the control regimen are notable because these toxic effects generally occur in early treatment cycles and can lead to treatment-induced morbidity and mortality.

Several issues must be considered in integrating this trial's data with data from other studies to define optimal treatment for this disease. The IFL regimen delivers FU via bolus injection; the FOLFOX program calls for infused FU over 2 days. Previous studies have demonstrated diminished toxicity with FU infusion compared with bolus administration, with a modest 1-month improvement in median survival [4,19]. The current study does not allow isolation of the relative independent contributions of oxaliplatin versus irinotecan and infused versus bolus FU.

Tournigand et al [20] randomly assigned 226 patients to oxaliplatin or irinotecan, both with infused FU/LV. Patients received both regimens in opposite sequence in a crossover design. The primary end point was time to progression after receiving both regimens. No statistically significant difference in time to progression or overall survival was observed between the treatment strategies.

Second-line chemotherapy likely contributed to overall survival. Because oxaliplatin was not readily available and because irinotecan was marketed in North America, more patients received irinotecan after discontinuing FOLFOX than received oxaliplatin after discontinuing IFL. Randomized studies have demonstrated modest but statistically significant survival advantages attributable to irinotecan after failure of FU-based therapy for advanced colorectal cancer—2.3 months compared with infused FU, and 2.7 months compared with best supportive care [21,22]. A 4% response rate reported for irinotecan plus FU/LV after FOLFOX suggests modest benefit from irinotecan after oxaliplatin and FU [20]. Availability of second-line therapy does not explain the increased response rate and time to tumor progression (as done in the sensitivity analysis) with FOLFOX, since these events were evaluated while patients were on initial therapy. The increase in time to progression remained statistically significant in sensitivity analyses in which patients were censored for progression when initial treatment was discontinued. The 19.5-month median survival observed in patients receiving FOLFOX (60% of whom received subsequent irinotecan) argues strongly that sequential treatment with all three agents benefits patients with this disease.

The finding that time to treatment discontinuation was not different in the control versus FOLFOX arm deserves consideration. More patients discontinued therapy on the control arm than the experimental arms because of progression or death; more patients on the experimental arms stopped because of adverse events, principally reversible hematologic toxicity and paresthesias. It seems likely that patients stopping therapy without progression will have an improved clinical course compared with those with progressive disease. This may explain the apparent contradiction inferred by the finding that similar times to treatment discontinuation between the arms contrasted with the differences in survival.

In conclusion, this study has demonstrated statistically significant improved response rate, time to disease progression, and overall survival for patients treated with a regimen of FOLFOX as compared with the control regimen of IFL. This improvement in efficacy, coupled with a favorable toxicity profile, suggests that FOLFOX should be considered a first-line standard of care for patients with advanced colorectal cancer, and one that is more active and better tolerated than either IFL or IROX. Phase III protocols comparing irinotecan with oxaliplatin, with both using infused FU/LV, are being activated through National Cancer Institute–funded cooperative oncology groups.

Acknowledgment

We thank the patients who enrolled onto the trial, the investigators who enrolled them, and the North Central Cancer Treatment Group Operations and Statistical Office personnel, including Jeannine A. Hadley, Carol A. Leonard, Linda G. Healy, and Erin M. Green.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Acted as a consultant within the last 2 years: Richard M. Goldberg, Sanofi-Synthelabo, Pharmacia Corp; Charles S. Fuchs, Sanofi-Synthelabo, Pharmacia Corp; Ramesh K. Ramanathan, Sanofi-Synthelabo, Pharmacia Corp; Stephen K. Williamson, Sanofi-Synthelabo, Pharmacia Corp; Daniel J. Sargent, Pharmacia Corp. Received more than $2,000 a year from a company for either of the last 2 years: Richard M. Goldberg, Sanofi-Synthelabo, Pharmacia Corp; Charles S. Fuchs, Sanofi-Synthelabo, Pharmacia Corp; Ramesh K. Ramanathan, Sanofi-Synthelabo, Pharmacia Corp.

REFERENCES

1. Jemal A, Thomas A, Murray T, et al: Cancer statistics, 2002. CA Cancer J Clin 52:23-47, 2002

2. Sobrero AF, Aschele C, Bertino JR: Fluorouracil in colorectal cancer: A tale of two drugs—Implications for biochemical modulation. J Clin Oncol 15:368-381, 1997

3. 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 10:896-903, 1992

4. de Gramont A, Bosset JF, Milan C, et al: Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: A French intergroup study. J Clin Oncol 15:808-815, 1997

5. Hsiang YH, Hertzberg R, Hecht S, et al: Camptothecin induces protein-linked DNA breaks via mammalian DNA topoisomerase I. J Biol Chem 260:14873-14878, 1985

6. Saltz LB, Cox JV, Blanke C, et al: Irinotecan Study Group: Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. N Engl J Med 343:905-914, 2000

7. Douillard JY, Cunningham D, Roth AD, et al: Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: A multicentre randomised trial. Lancet 355:1041-1047, 2000

8. Woynarowski JM, Chapman WG, Napier C, et al: Sequence- and region-specificity of oxaliplatin adducts in naked and cellular DNA. Mol Pharmacol 54:770-777, 1998

9. Rixe O, Ortuzar W, Alvarez M, et al: Oxaliplatin, tetraplatin, cisplatin, and carboplatin: Spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. Biochem Pharmacol 52:1855-1865, 1996

10. de Gramont A, Figer A, Seymour M, et al: Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938-2947, 2000

11. Wasserman E, Cuvier C, Lokeic F, et al: Combination of oxaliplatin plus irinotecan in patients with gastrointestinal tumors: Results of two independent phase I studies with pharmacokinetics. J Clin Oncol 17:1751-1759, 1999

12. Scheithauer W, Kornek GV, Raderer M, et al: Combined irinotecan and oxaliplatin plus granulocyte colony-stimulating factor in patients with advanced fluoropyrimidine/leucovorin-pretreated colorectal cancer. J Clin Oncol 17:902-906, 1999

13. Morton RF, Goldberg RM, Sargent DJ, et al: Oxaliplatin (OXAL) or CPT-11 combined with 5FU/leucovorin (LV) in advanced colorectal cancer (CRC): An NCCTG/CALGB study. Proc Am Soc Clin Oncol 20:125, 2001 (abstr)

14. Sargent DJ, Niedzwiecki D, O'Connell MJ, et al: Recommendation for caution with irinotecan, fluorouracil, and leucovorin for colorectal cancer. N Engl J Med 345:144-145, 2001

15. O'Brien PC, Fleming TR: A multiple testing procedure for clinical trials. Biometrics 35:549-556, 1979

16. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958

17. Cox DR: Regression models and life-tables. J R Stat Soc 34B:187-220, 1972

18. Giacchetti S, Perpoint B, Zidani R, et al: Phase III multicenter randomized trial of oxaliplatin added to chronomodulate fluorouracil-leucovorin as first-line treatment of metastatic colorectal cancer. J Clin Oncol 18:136-147, 2000

19. Meta-Analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. J Clin Oncol 16:301-308, 1998

20. Tournigand C, Louvet C, Quinax E, et al: FOLFIRI followed by FOLFOX versus FOLFOX followed by FOLFIRI in metastatic colorectal cancer (MCRC): Final results of a phase III study. Proc Am Soc Clin Oncol 20:124, 2001 (abstr)

21. Cunningham D, Pyrhonen S, James RD, et al: Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. Lancet 352:1413-1418, 1998

22. Rougier P, Van Cutsem E, Bajetta E, et al: Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. Lancet 352:1407-1412, 1998