VOLUME 24 · NUMBER 22 · AUGUST 1 2006

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial Comparing 4-Day Chronomodulated Therapy Versus 2-Day Conventional Delivery of Fluorouracil, Leucovorin, and Oxaliplatin As First-Line Chemotherapy of Metastatic Colorectal Cancer: The European Organisation for Research and Treatment of Cancer Chronotherapy Group

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Submitted February 27, 2006; accepted May 17, 2006.

Supported in part by a grant from Sanofi Pharma, which also provided oxaliplatin for patients until approval of the drug. Supported by Association pour la Recherche sur le temps Biologique et la Chronotherapie (ARTBC) Internationale and Cephyten.

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

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0732-183X/06/2422-3562/$20.00

DOI: 10.1200/JCO.2006.06.1440

ABSTRACT

Purpose
In two previous randomized trials, the adjustment of chemotherapy delivery to circadian rhythms improved tolerability and anticancer activity compared with constant-rate infusion during 5 days in patients with metastatic colorectal cancer.

Patients and Methods
For this multicenter randomized trial, it was hypothesized that a chronomodulated infusion of fluorouracil, leucovorin, and oxaliplatin for 4 days (chronoFLO4) would improve survival by 10% compared with conventional 2-day delivery of the same drugs (FOLFOX2). Patients were treated every 2 weeks with intrapatient dose escalation.

Results
Baseline characteristics were similar in both arms for the 564 patients (36 institutions, 10 countries). Median survival was 19.6 months (95% confidence limit [CL] = 18.2, 21.2) with chronoFLO4 and 18.7 months with FOLFOX2 (95% CL = 17.7, 21.0; P = .55). The main dose-limiting toxicities were diarrhea for chronoFLO4 and neutropenia for FOLFOX2. The analysis of survival predictors showed that sex was the single most important factor (P = .001). In women, the risk of an earlier death with chronoFLO4 was increased by 38% compared with FOLFOX2, with median survival times of 16.3 and 19.1 months (P = .03), respectively. In men, the risk of death was decreased by 25% with chronoFLO4 compared with FOLFOX2, with median survival times of 21.4 and 18.3 months (P = .02), respectively.

Conclusion
Both regimens achieved similar median survival times more than 18 months with an acceptable toxicity. The chronomodulated schedule produced a survival advantage over FOLFOX in men. The strong sex dependency of optimal scheduling of fluorouracil, leucovorin, and oxaliplatin calls for translational investigations of determinants related to the patient's molecular clock.

J Clin Oncol 24:3562-3569. © 2006 by American Society of Clinical Oncology

INTRODUCTION

Finding new anticancer drugs and defining their optimal delivery schedule is the mainstay of developmental therapeutics. Chronotherapeutics aim to determine the most active treatment schedule, based on the adjustment of drug delivery to the 24-hour rhythms generated by the circadian timing system.[1,2]

Mammalian cells contain a molecular clock with fine-tuned feedback loops of 12 specific genes.[2] This molecular clock regulates the cell division cycle, apoptosis, gene expression, and DNA repair, as well as several signaling and metabolic pathways.[3-5] As a result, anticancer chemotherapy at specific circadian times can reduce toxicities for host cells and enhance efficacy against cancer cells.[1] The International Organisation for Cancer Chronotherapy has contributed to the progress in colorectal cancer in particular through the initial demonstration of the activity of oxaliplatin (Eloxatin; Sanofi Recherche,

Montpellier, France), a drug initially rejected for excessive toxicity and poor activity in this disease.[6] Chronotherapy has been implemented in nonhospitalized cancer patients through the use of programmable-in-time multichannel pumps.[1] The relevance of circadian rhythms for malignant diseases is further supported by recent experimental evidence in which tumor progression resulted from the deregulation of the circadian timing system through clock gene mutation or environmental alterations.[3-5]

The rationale for the current study is based on several clinical trials by our group in which the activity and safety of a chronomodulated delivery of combined fluorouracil (FU), leucovorin (LV), and oxaliplatin (chronoFLO) was established. In two multicenter randomized trials, response rate was increased and toxicity was less severe in the patients receiving chronomodulated delivery compared with constant-rate infusion. The median survival was close to 17 months on both schedules.[7,8] These results were in contrast to those achievable with the standard regimen at that time of FU-LV.[9]

The activity of oxaliplatin was then confirmed in a multicenter trial showing an increase response rate and progression-free survival (PFS) but no survival advantage in the oxaliplatin arm.[10] An attempt was made to enhance efficacy through an increase in dose density. The three-drug chronomodulated schedule was administered for 4 days with 10 days off and the FU dose was escalated by ~40% (chronoFLO4). This schedule increased the objective response rate to 66% and median survival to 18.5 months in a phase II trial.[11] In the meantime, the regimen of constant-rate infusion of FU, LV, and oxaliplatin for 2 days (FOLFOX2) provided good activity and acceptable tolerability.[12]

These data led the Chronotherapy Group of the European Organisation for Research and Treatment of Cancer (EORTC) to conduct a pragmatic comparison trial between these active regimens with the hypothesis that chronoFLO4 would increase survival compared with FOLFOX2. Initial drug doses per course were the same in both schedules. Intrapatient dose escalation of FU was planned to deliver both regimens near individual maximum dose-intensity.

PATIENTS AND METHODS

This multicenter, randomized, two-arm, phase III study was approved by the review board of the EORTC and by the ethics review boards at the participating centers.

The calculated target sample size of 554 patients assumed that the survival rate at 2 years would be 40% in chronoFLO4 arm and 30% in the FOLFOX2 arm. This study had an 80% power at a significance level of .05 to detect this 10% increase in the 2-year survival in favor of chronoFLO4, assuming the occurrence of 430 deaths.

Admission criteria included metastatic colorectal cancer; performance status (PS) ≤ 2; written informed consent; histologic proof of colorectal adenocarcinoma; age ranging from 18 to 76 years; adequate hematologic, renal, and hepatic functions; measurable metastatic lesions (largest diameter > 20 mm); no brain metastases; and no prior chemotherapy or radiotherapy for metastatic disease. Adjuvant chemotherapy had to be completed ≥ 6 months before the diagnosis of metastatic disease.

Random assignment to treatment was performed at the EORTC Data Center using the minimization technique.[13] Patients assigned to chronoFLO4 received a 4-day course of chronomodulated infusions of FU-LV from 2215 to 0945 hours with a peak at 0400 hours, and oxaliplatin from 1015 to 2145 hours with a peak at 1600 hours (Fig 1A). Treatment was administered using a four-reservoir, multichannel, programmable in-time pump (Melodie, Aguettant, France) in an outpatient setting.[1,7] Patients assigned to FOLFOX2 received oxaliplatin and LV as a 2-hour infusion on day 1 and LV only on day 2, starting between 0900 and 1600 hours. The FU infusion was delivered at a constant rate for 22 hours on days 1 and 2 (Fig 1B). Courses were repeated every 14 days.[12] Patients were stratified according to PS, liver involvement (none, $< 25\%$, or $\geq 25\%$), and center. All patients received the same doses of FU (3,000 mg/m^2), LV (1,200 mg/m^2), and oxaliplatin (100 mg/m^2) on the first course. An escalation of FU by 400 mg/m^2/course on the second and by 200 mg/m^2 on the third course was planned if no grade ≥ 2 toxicity had occurred. In patients with grade 2 toxicity, the doses remained unchanged. Dose reductions were planned for patients with grade 3 or 4 toxicities. The toxicity on each course was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Peripheral sensory neuropathy was graded according to our specific scale.[8]

The evaluation of patients for eligibility included a physical examination; computed tomography scan of the abdomen, pelvis, and thorax; a CBC; and serum chemistry including carcinoembryonic antigen and CA 19-9.[7-10] Response was assessed every fourth treatment course and defined according to the WHO criteria. Independent radiology assessment was done for patients considered as responders by the investigator. Patients were taken off study for progressing disease, lack of full recovery from severe toxicity, or complete surgical resection of metastases.

The primary end point was the 2-year survival rate. Secondary end points were PFS, objective response rate, safety, and quality of life. Overall survival (OS) was defined as the time from random assignment to death, and PFS was computed from random assignment to progression or death, whichever occurred first. Patients who discontinued therapy for reasons other than death or progression were censored at the dropout date. OS and PFS were analyzed

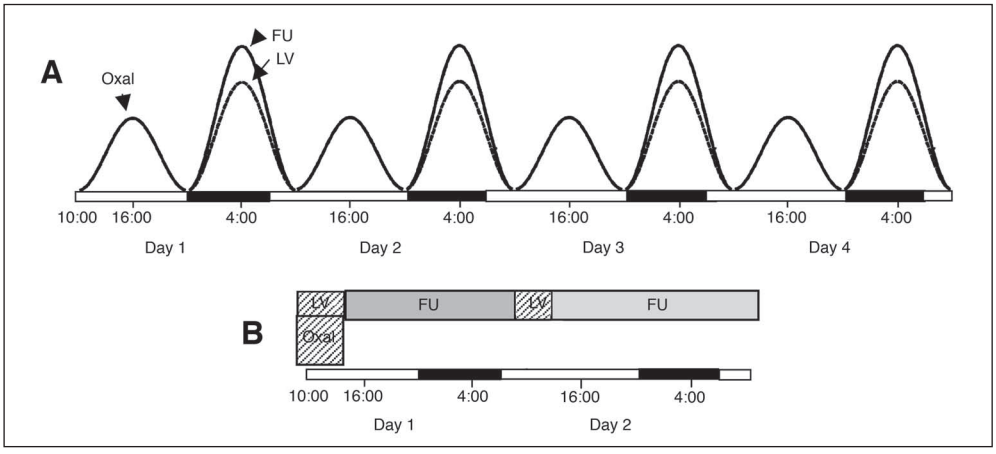

Fig 1. Treatment schedules combining oxaliplatin (Oxal), fluorouracil (FU), and leucovorin (LV) administered as (A) a chronomodulated infusion during 4 days (chronoFLO4) or (B) conventional infusion during 2 days (FOLFOX2). The abscissa represents alternating spans of 8 hours of darkness, corresponding to the average rest span at night, and 16 hours of light, corresponding to the average wakefulness at daytime, over the course of chemotherapy delivery.

according to Kaplan-Meier, with two-sided log-rank statistics. The Cox proportional hazards model was fitted to adjust for stratification factors and other confounding variables.

The comparisons of the response rates, grade 3 or 4 toxicity rates, and other proportions were performed using the two-sided Fisher's exact test. Continuous measurements were compared with the two-sided Wilcoxon rank test. All efficacy analyses were performed on the intent-to-treat population.

Prognostic and predictive factors of survival and PFS were investigated using Cox proportional hazards model and two-sided log-rank statistics. Peto's interaction tests were computed and the Cox proportional hazards model with treatment per factor interaction term were fitted. For binary data, logistic regression models with interaction treatment per factor term and stepwise selection method were fitted. For continuous measurements, general linear models with treatment per factor interaction term were used.

RESULTS

Patient Demographics and Treatment Delivery

From October 1998 to February 2002, 564 patients from 36 centers in 10 countries (Austria, Belgium, Canada, France, Germany, United Kingdom, Greece, Italy, Norway, and Portugal) were enrolled. The patient characteristics were well balanced between study arms (Table 1; Fig 2). Twenty-eight patients (5%) were ineligible (FOLFOX2, 15 patients; chronoFLO4, 13 patients).

Median follow-up was 40.3 months for FOLFOX2 and 42.7 months for chronoFLO4. A total number of 2,941 courses of FOLFOX2 and 2,806 courses of chronoFLO4 were given. Patients received a median number of 10 courses of either schedule.

Pump dysfunctions were reported for three patients receiving FOLFOX2 and 13 patients receiving chronoFLO4. Early withdrawal occurred within 2 months of treatment onset in 37 patients receiving FOLFOX2 and 54 patients receiving chronoFLO4 (Fisher's exact test, $P = .02$); the main reasons were tumor progression (FOLFOX2, six patients; chronoFLO4, 15 patients) and toxicity (seven and 13 patients, respectively).

The planned FU dose escalation during the initial three courses was performed in 301 patients (53.4%; 151 patients [53.5%] receiving FOLFOX2, and 142 patients [50%] receiving chronoFLO4). The median dose-intensity during the 12 initial treatment courses was similar for FOLFOX2 and chronoFLO4 for both FU (1.4 *v* 1.3 g/m^2/wk) and oxaliplatin (38 *v* 38 mg/m^2/wk).

Table 1. Patient Characteristics

Characteristic	FOLFOX2 (n = 282) No. of Patients	%	chronoFLO4 (n = 282) No. of Patients	%
Age, years				
Median	62		62	
Range	31.8-76		22.3-76	
Sex				
Female	112	40	114	40
Male	170	60	168	60
Performance status (WHO)				
0	139	49	134	47
1	116	41	115	41
2	27	10	33	12
Initial Dukes' stage				
A/B	33	11	25	9
C	39	14	46	16
D (synchronous metastases)	207	73	210	75
Unknown	3		1	
Colon	213	76	217	77
Rectum	69	24	65	23
Previous adjuvant treatment				
Chemotherapy	48	17	54	19
Radiotherapy	18	6	26	9
Previous surgery of metastases	14	5	14	5
No. of metastases				
0	1		3	
1	142	50	140	50
2	90	32	101	36
≥ 3	48	17	38	13
Unknown	1		0	
Organs involved				
Liver	242	86	241	85
Lung	104	37	105	37
Percentage of liver involvement				
≤ 25	129	46	137	49
> 25	113	40	104	37
CEA, ng/mL				
≤ 10	72	25	73	26
> 10	187	66	181	64
Unknown	23	9	28	10
CA 19-9, U/mL				
≤ 37	67	24	76	27
> 37	134	47	127	45
Unknown	81	29	79	28

Abbreviations: FOLFOX2, oxaliplatin, fluorouracil, and leucovorin administered during 2 days; chronoFLO4, chronomodulated oxaliplatin, fluorouracil, and leucovorin administered during 4 days; CEA, carcinoembryonic antigen.

Safety

There were three treatment-related deaths (FOLFOX2, one patient; chronoFLO4, 2 patients). Grade 3 or 4 toxicity of any kind occurred in 63.9% of the patients receiving FOLFOX2 (14.2% of the courses) and 63.0% of the patients receiving chronoFLO4 (16.1% of the courses; Table 2). The main acute toxicities were neutropenia and diarrhea. Severe neutropenia occurred in nearly three-fold as many patients receiving FOLFOX2 compared with chronoFLO4, whereas diarrhea was three-fold less frequent in patients receiving FOLFOX2 compared with chronoFLO4. Other GI and skin toxicities occurred more frequently in patients receiving chronoFLO4 compared with FOLFOX2. The incidence of peripheral sensory neuropathy was similar in both arms.

Response, Surgery for Metastases, and PFS

Independent radiology assessment was performed for the 144 responding patients receiving FOLFOX2 and the 145 responding patients receiving chronoFLO4. The objective response rates were similar in both treatment modalities (Table 3). In addition, 22 patients (7.8%) receiving FOLFOX2 and 25 patients (8.9%) receiving chronoFLO4 had a partial response that could not be confirmed, mostly because they underwent metastases surgery immediately after documentation of the best response. Median PFS was 8.4 months for both treatment arms, with a hazard ratio close to 1 (Table 3). Surgical removal of residual metastases after chemotherapy was attempted in 50 patients receiving each schedule. Partial hepatectomy was done in 47 patients receiving FOLFOX2 and 50 patients receiving chronoFLO4. A complete macroscopic resection was performed for 35

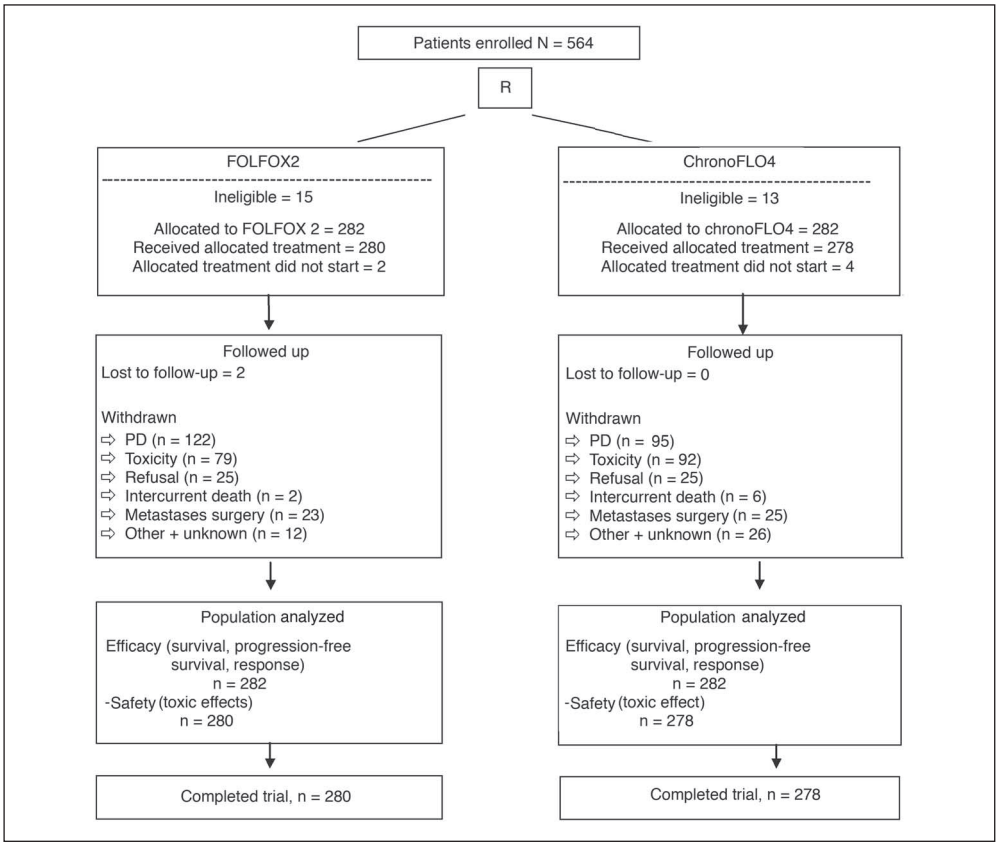

Fig 2. Trial profile. R, randomized assignment; FOLFOX2, oxaliplatin, fluorouracil, and leucovorin administered during 2 days; chronoFLO4, chronomodulated oxaliplatin, fluorouracil, and leucovorin administered during 4 days; PD, progressive disease.

patients receiving FOLFOX2 and 37 patients receiving chronoFLO4, with a similar proportion of tumor-free margins. A complete histologic response was documented for three patients receiving FOLFOX2 compared with eight patients receiving chronoFLO4.

Survival

Median survival time was 18.7 months (95% confidence limit [CL] = 17.7, 21.0) for patients receiving FOLFOX2 and 19.6 months (95% CL = 18.2, 21.2) for patients receiving chronoFLO4 ($P = .55$), a difference corresponding to a hazard ratio of 0.95 (95% CL = 0.79 to

Table 2. Incidence of Grade 3-4 Toxicity per Patient in the Safety Population

Toxicity	FOLFOX2 (n = 280) No. of Patients	%	chronoFLO4 (n = 278) No. of Patients	%	*P*
Neutropenia	71	25.3	22	7.9	< .001
Any hematologic toxicity	82	29.3	31	11.2	< .001
Diarrhea	31	11	82	29.5	< .001
Mucositis	19	6.8	41	14.8	.004
Hand-foot syndrome	5	1.8	33	11.9	< .001
Asthenia	21	7.5	44	15.8	.004
Peripheral sensory neuropathy	82	29	76	27	NS
Any main toxicity	179	63.9	175	63.0	NS

Abbreviations: FOLFOX2, oxaliplatin, fluorouracil, and leucovorin administered during 2 days; chronoFLO4, chronomodulated oxaliplatin, fluorouracil, and leucovorin administered during 4 days; NS, not significant.

Table 3. Response Rate, Metastases Surgery, and Progression-Free Survival According to Treatment Schedule

Variable	Schedule: FOLFOX2 (n = 282) No. of Patients	%	chronoFLO4 (n = 282) No. of Patients	%
Response				
Complete	6	2.1	4	1.4
Partial confirmed	121	42.2	115	40.8
Objective responses	127	44.3	119	42
Exact 95% CL	39, 51		36, 48	
Metastases resection				
All attempts with curative intent	50	17.7	50	17.7
Macroscopically complete (R0)	35	12.4	37	13.1
Histologically complete	3	1.1	8	2.8
Margins				
Free	24	8.5	23	8.2
Involved	2	0.7	3	1.1
Unknown	6	2.1	3	1.1
Radiofrequency alone	1	0.3	1	0.3
Progression-free survival				
Median	8.4		8.4	
95% CL, months	7.8, 9.4		7.5, 9.4	

NOTE. No significant difference was found between groups.
Abbreviations: FOLFOX2, oxaliplatin, fluorouracil, and leucovorin administered during 2 days; chronoFLO4, chronomodulated oxaliplatin, fluorouracil, and leucovorin administered during 4 days; CL, confidence limit.

1.14; Fig 3A). Survival rates at 2 years were 36.9% (95% CL = 31.2, 42.5) for patients receiving FOLFOX2 and 37.0% (95% CL = 31.4, 42.7) for patients receiving chronoFLO4.

Seven clinical factors were found to be prognostic for survival at multivariate analysis. Poor prognosis was associated with a PS of 1 or 2 ($P = .003$), two or more metastatic sites ($P < .0001$), analgesics at entry ($P < .0001$), abnormal initial granulocyte count ($P = .0002$), carcinoembryonic antigen more than 10 ng/mL ($P = .01$), CA 19-9 more than 37 U/mL ($P = .002$), and AST more than 36 U/L ($P = .0005$). The treatment effect remained similar when the data were adjusted for potential prognostic factors selected by the Cox's proportional hazards regression model.

Predictive Factors of Survival

Of the 12 potential factors that were considered, sex stood out as the single most important predictor of survival. The hazard ratio of deaths was increased by 38% in the women administered chronoFLO4, whereas it was reduced by 25% in the men receiving this modality (Fig 3B). The median survival of the 226 women receiving FOLFOX2 was 19.1 months compared with 16.3 months for those receiving chronoFLO4 ($P = .027$), with 2-year survival rates of 40.8% and 27.1%, respectively (Fig 3C). Conversely, the median survival of the 338 men receiving FOLFOX2 was 18.3 months and 21.4 months for those receiving chronoFLO4 ($P = .018$), with 2- year survival rates of 34.3% and 43.6%, respectively (Fig 3D). The

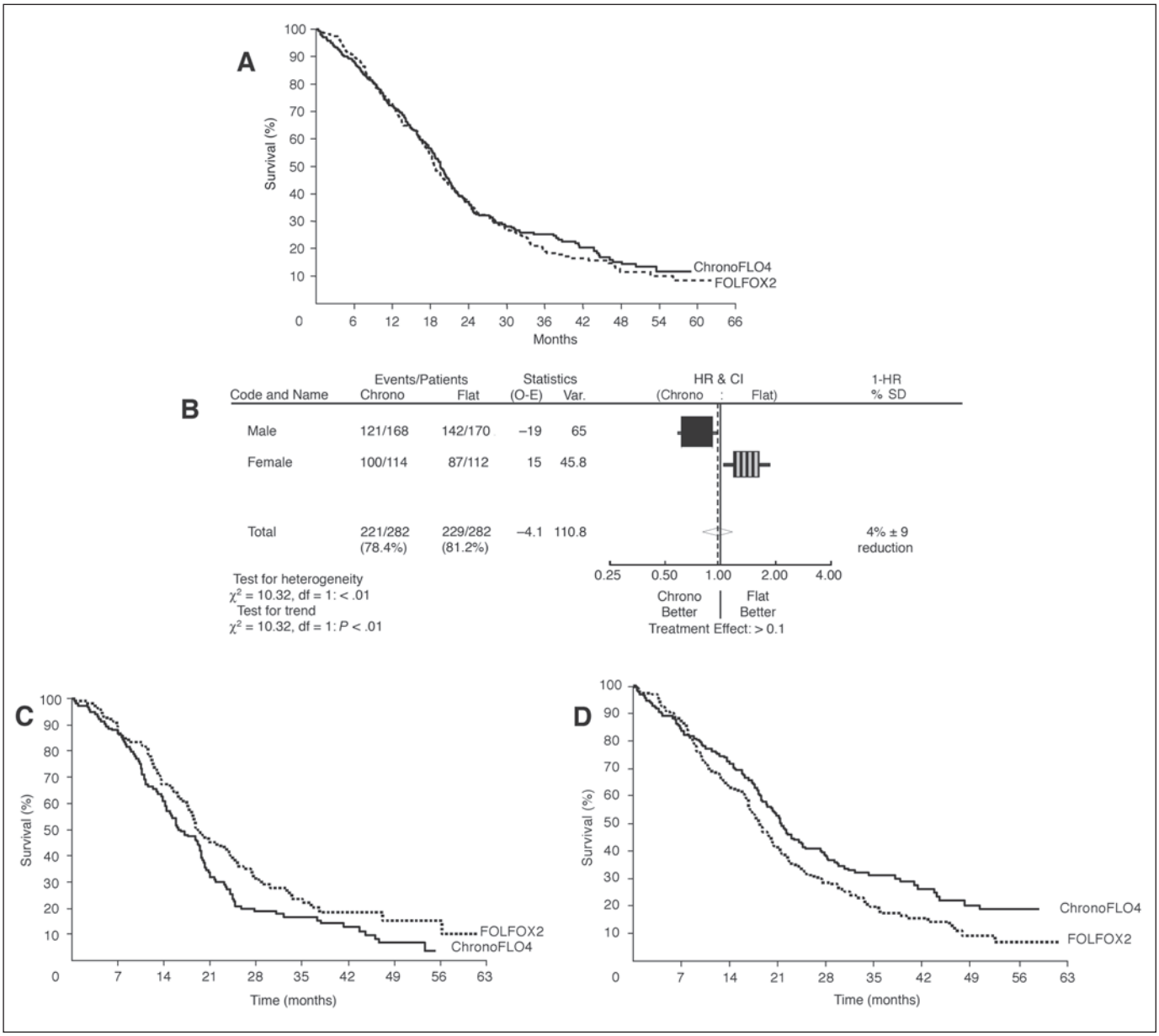

Fig 3. Drug delivery schedule for survival. (A) overall survival ($P = .549$); (B) Forrest plot of interaction between schedule and sex ($P < .01$); (C) overall survival of women ($P = .0269$); (D) overall survival of men ($P = .0183$). For (A), (C), and (D), (· · ·) represents oxaliplatin, fluorouracil, and leucovorin administered during 2 days (FOLFOX2) and (——) represents chronomodulated oxaliplatin, fluorouracil, and leucovorin administered during 4 days (chronoFLO4). Var., variance; HR, hazard ratio; SD, standard deviation; Chrono, chronoFLO4.

sex-schedule interaction test was highly significant ($P < .001$; Fig 3B). Patients' characteristics according to sex were well balanced except for age and PS. Age ≤ 50 years and PS of 1 or 2 were more frequent in women than in men (21% *v* 14%; and 59% *v* 46.5%, respectively). After stratification for age and PS, the interaction tests were not found significant ($P > .1$) because of a lack of power but presented the same trend for a higher efficacy in men treated with chronoFLO4 in the different age and PS strata. In a Cox proportional hazards model, a sex-schedule interaction term was found significant in presence of the PS, age, number of metastatic sites, and percentage of liver involvement (Table 4).

Other Sex-Related Effects

The incidence of grade 3 or 4 main toxicities was greater by 15.3% in women compared with men (95% CL = 7.5, 23.2). The dose-intensities of both FU and oxaliplatin were lower in women than in men. The magnitude of the difference in schedule-dependent toxicity was larger in men compared with women. The response rate did not differ significantly between female and male patients. A significant sex-schedule interaction was found for PFS ($P = .008$), with median PFS in women who received FOLFOX2 of 8.6 months compared with 6.9 months in women who received chronoFLO4 ($P = .02$), whereas the median PFS in men who received FOLFOX2 was 8.4 months compared with 9.4 months in men who received chronoFLO4 ($P = .18$).

DISCUSSION

Our group provided the initial demonstrations of the clinical activity of oxaliplatin, synergistic activity with FU-LV, better tolerability and antitumor activity of the three drugs through chronomodulated administration, and surgical resection of previously unresectable colorectal cancer metastases.[6-8,10,11,14] Most of these achievements have been confirmed by other groups, resulting in median survival times of 15 to 20 months in patients with metastatic colorectal cancer.[15,16]

We compared two delivery schedules of oxaliplatin, FU, LV regimen for metastatic colorectal cancer with adequate power to address survival as the main end point. A difference in the toxicity profiles of both schedules was observed, with more neutropenia for FOLFOX2 and more diarrhea for chronoFLO4. The reduced bone marrow toxicity for chronoFLO4 could result from the lowest proliferation of bone marrow cells at night when the delivery rate of S-phase–specific FU was the highest.[17] Both schedules achieved similar response rate and PFS.

Median survival times were close to 19 months in both arms, supporting that OS may not be the most appropriate end point to assess the efficacy of a first-line treatment in metastatic colorectal cancers, given that subsequent chemotherapy lines and metastases surgery also influence outcome.[16]

We assumed that individual patient characteristics could predict for a survival benefit of chronoFLO4 in our trial. Using three different statistical methods, sex was the single predictor of survival, independent of baseline patient characteristics. Women did significantly worse, whereas men did significantly better when receiving chronoFLO4 compared with FOLFOX2. These differences could not be ascribed to schedule-dependent differences in dose-intensities, which were lower on both schedules in women compared with men.

Why would the 10% survival benefit from chronoFLO4 over FOLFOX2 that was expected in the whole patient population be limited to men? Because the difference in survival was only observed in the chronotherapy arm, the responsible metabolic and/or genetic mechanism must influence variables that are modified in time. We propose the following hypotheses.

First, a different genotypic profile between males and females with colorectal cancer could exist. Colorectal cancers displayed a greater incidence of microsatellite instability, a favorable prognostic factor for survival in females compared with males.[18,19] Sex-dependent alterations were also found for cell cycle regulatory genes such as *P16*, *P53*, *EGFR*, and *E2RB*.[20,21] Thus, a different genotypic profile could characterize colorectal cancers in women compared with men, especially for genes responsible for cell cycle, apoptosis, and DNA repair, 10% of which are controlled by the molecular clock.[3] Sex has been reported as a predictor of survival for non–small-cell lung cancer[22] and melanoma.[23]

Second, excessive toxicity has been observed in women treated with FU-based chemotherapy. In both arms hematologic and nonhematologic toxicities were greater in women than in men, a finding consistent with previous reports on FU or FOLFOX regimens.[15,24,25] This difference may be due to reduced FU clearance and dihydropyrimidine deshydrogenase (DPD) activity in women compared with men.[26,27] A sex-dependent polymorphism of the *DPD* gene may also account for this.[28] The lower expression of DPD in the tumors in women could increase susceptibility of female colorectal cancers to conventional FU delivery.[29]

Third, sex dependency of circadian pharmacology has been observed. The tolerability of FU relates to FU clearance and DPD activity, whereas reduced glutathione levels affect oxaliplatin tolerability.[26-29] These determinants of chemotherapy toxicities display circadian rhythms in cancer patients, with large amplitudes in males and damped or ablated amplitudes in females.[26] When several peak times for drug delivery were studied in colorectal cancer, optimal chemotherapy timing for toxicity occurred within a 3-hour window for men (ie, 1300 to 1600 hours for oxaliplatin and 0100 to 0400 hours for FU-LV, compared with a 12-hour wide

Table 4. Cox Proportional Hazards Model of Survival Including the Interaction Between Sex and Treatment Schedule and the Main Prognostic Factors

Variable	*P*	Hazard Ratio	95% CI
Female and chronoFLO4 (*v* male or FOLFOX2)	.005	1.73	1.18 to 2.53
chronoFLO4 (*v* FOLFOX2)	.012	0.73	0.57 to 0.93
Female (*v* male)	.32	0.87	0.66 to 1.14
PS > 0 (*v* PS = 0)	< .0001	1.72	1.42 to 2.08
Age > 50 (*v* ≤ 50)	.67	0.95	0.74 to 1.21
One metastatic site (*v* > 1)	< .0001	0.60	0.50 to 0.73
Liver involvement (no *v* ≤25% *v* > 25%)	.02	1.19	1.03 to 1.38

Abbreviations: chronoFLO4, chronomodulated oxaliplatin, fluorouracil, and leucovorin administered during 4 days; FOLFOX2, oxaliplatin, fluorouracil, and leucovorin administered during 2 days.

window in women).[30] ChronoFLO4 would be properly timed more frequently in men than in women, resulting in better therapeutic index in men on this schedule.

Fourth, high-dose chemotherapy altered the circadian timing system through mechanisms possibly involving the release of growth factors and cytokines.[31] Transforming growth factor alpha and interleukin-6 modified the circadian timing system by altering hypothalamic coordination and clock genes expression. High levels of both cytokines were associated with circadian rhythm alterations and poor survival in patients with metastatic colorectal cancer.[32] A poorer stability of the circadian time structure in women compared with men was supported by a more frequent suppression of melatonin rhythm by light at night[33] and a larger cortisol response to stress.[34] In turn, an abnormal circadian time structure clearly has been associated with a more rapid cancer progression and poorer survival both in rodents and in cancer patients.[3,5,35]

In summary, this is the first clinical trial of chronotherapy to address survival with an adequate sample size. No survival difference was found as a function of treatment schedule in the overall population, but a sex dependency for the optimal schedule was observed, with a median survival with chronotherapy ranging from 16.3 months in women to 21.4 months in men. The large sex-dependent effects of chronoFLO4 call for confirmation in clinical trials incorporating the recently available new targeted agents. Ongoing translational studies of molecular determinants of optimal schedule could reveal differential expression patterns and genotypes of clock genes or clock-controlled genes that regulate cell cycle, apoptosis, repair, and drug pharmacology.

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Acknowledgment

We thank the patients, colleagues, and panel radiologists who participated in this study.

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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