

Original Article

Fatigue and Weight Loss Predict Survival on Circadian Chemotherapy for Metastatic Colorectal Cancer

Pasquale F. Innominato, MD, PhD^{1,2,3,4}; Sylvie Giacchetti, MD, PhD^{1,2,3,5}; Thierry Moreau, PhD^{6,7}; Georg A. Bjarnason, MD, PhD⁸; Rune Smaaland, MD, PhD⁹; Christian Focan, MD, PhD¹⁰; Carlo Garufi, MD¹¹; Stefano Iacobelli, MD¹²; Marco Tampellini, MD¹³; Salvatore Tumolo, MD¹⁴; Carlos Carvalho, MD¹⁵; Abdoulaye Karaboué, MD^{1,2}; Antoine Poncet, MSc^{1,2,17}; David Spiegel, MD, PhD¹⁶; and Francis Lévi, MD, PhD^{1,2,3}; for the International Association for Research on Time in Biology and Chronotherapy (ARTBC) Chronotherapy Group

BACKGROUND: Chemotherapy-induced neutropenia has been associated with prolonged survival selectively in patients on a conventional schedule (combined 5-fluorouracil, leucovorin, and oxaliplatin [FOLFOX2]) but not on a chronomodulated schedule of the same drugs administered at specific circadian times (chronoFLO4). The authors hypothesized that the early occurrence of chemotherapy-induced symptoms correlated with circadian disruption would selectively hinder the efficacy of chronotherapy. **METHODS:** Fatigue and weight loss (FWL) were considered to be associated with circadian disruption based on previous data. Patients with metastatic colorectal cancer ($n = 543$) from an international phase 3 trial comparing FOLFOX2 with chronoFLO4 were categorized into 4 subgroups according to the occurrence of FWL or other clinically relevant toxicities during the initial 2 courses of chemotherapy. Multivariate Cox models were used to assess the role of toxicity on the time to progression (TTP) and overall survival (OS). **RESULTS:** The proportions of patients in the 4 subgroups were comparable in both treatment arms ($P = .77$). No toxicity was associated with TTP or OS on FOLFOX2. The median OS on FOLFOX2 ranged from 16.4 (95% confidence limits [CL], 7.2-25.6 months) to 19.8 months (95% CL, 17.7-22.0 months) according to toxicity subgroup ($P = .45$). Conversely, FWL, but no other toxicity, independently predicted for significantly shorter TTP ($P < .0001$) and OS ($P = .001$) on chronoFLO4. The median OS on chronoFLO4 was 13.8 months (95% CL, 10.4-17.2 months) or 21.1 months (95% CL, 19.0-23.1 months) according to presence or absence of chemotherapy-induced FWL, respectively. **CONCLUSIONS:** Early onset chemotherapy-induced FWL was an independent predictor of poor TTP and OS only on chronotherapy. Dynamic monitoring to detect early chemotherapy-induced circadian disruption could allow the optimization of rapid chronotherapy and concomitant improvements in safety and efficacy. *Cancer* 2013;119:2564-73. © 2013 American Cancer Society.

KEYWORDS: colorectal cancer; chemotherapy; circadian; toxicity; prognostic factor.

INTRODUCTION

The correlation between chemotherapy-induced toxicity and efficacy has been investigated extensively in patients with various cancers at different disease stages. Consequently, the current thinking is that adverse events are valid surrogate markers of adequate chemotherapy exposure.¹ Thus, clinical studies have repeatedly demonstrated that a lack of drug-specific toxicities is associated with poor survival outcomes.²⁻⁹ For instance, neutropenia was reported as an independent predictor of prolonged survival in patients receiving chemotherapy for metastatic colorectal cancer.^{5,10} We recently

Corresponding author: Francis Lévi, MD, PhD, INSERM U 776 "Rythmes Biologiques et Cancers," Hôpital Paul Brousse, 14 avenue P.V. Couturier, 94807 Villejuif Cedex, France; Fax: (011) 33 1 45 59 36 02; francis.levi@inserm.fr

¹National Institute for Health and Medical Research (INSERM) Unit 776, "Biological Rhythms and Cancers," Villejuif, France; ²Medical Research Unit (UMR) S0776, Paris South University, Orsay, France; ³Chronotherapy Unit, Department of Oncology, Public Hospital System of Paris (APHP), Paul Brousse Hospital, Villejuif, France; ⁴Faculty of Medicine, Paris South University, le Kremlin-Bicêtre, France; ⁵Breast Diseases Unit, Department of Medical Oncology, APHP, St. Louis Hospital, Paris, France; ⁶INSERM Center for Research in Epidemiology and Population Health, Unit 1018, Villejuif, France; ⁷UMR S1018, Paris South University, Villejuif, France; ⁸Department of Oncology, Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada; ⁹Department of Oncology, Stavanger University Hospital and Institute of Medicine, University of Bergen, Bergen, Norway; ¹⁰Department of Oncology, St. Joseph Clinics, Liège, Belgium; ¹¹Department of Oncology, Regina Elena Institute, Rome, Italy; ¹²Department of Oncology and Neurosciences, University "G. d'Annunzio" Medical School, Chieti, Italy; ¹³Department of Oncology, San Luigi Gonzaga Hospital, Orbassano, Italy; ¹⁴Department of Oncology, Santa Maria degli Angeli Hospital, Pordenone, Italy; ¹⁵Department of Oncology, F. Fonseca Hospital, Amadora, Portugal; ¹⁶Center on Stress and Health, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, United States of America.

Antoine Poncet's current address: CRC and Division of Clinical Epidemiology, Department of Health and Community Medicine, University of Geneva and University Hospitals of Geneva, Switzerland.

We sincerely thank all of the other investigators who enrolled patients in the European Organization for Research and Treatment of Cancer (EORTC) 05963 trial, Pierre-Antoine Dugué for his paramount help in updating the database, and Marie-Ange Lentz from the EORTC Data Center for her excellent data managing efforts.

DOI: 10.1002/cncr.28072, **Received:** December 21, 2012; **Revised:** February 7, 2013; **Accepted:** February 25, 2013, **Published online** April 30, 2013 in Wiley Online Library (wileyonlinelibrary.com)

confirmed this finding in patients who were receiving a conventional schedule of 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX2) in an international randomized trial.¹⁰ However, no positive relation between neutropenia and survival was observed in patients who were receiving a circadian-based schedule involving the chronomodulated delivery of the same drugs at selected times of day or night (chronoFLO4).¹⁰ Moreover, the delivery of chronoFLO4 significantly prolonged overall survival (OS) in men compared with FOLFOX2, but it significantly reduced survival in women.¹¹ These findings were confirmed in a meta-analysis of 3 international randomized trials.¹² Experimental data indeed support paying careful and specific attention to optimal circadian dosing of anticancer drugs, and maximal antitumor efficacy usually results from chemotherapy administered near the circadian time corresponding to best tolerability.¹³ Circadian rhythms are generated within each cell by molecular clocks, which consist of interwoven transcription/translation feedback loops.^{13,14} The molecular clocks, in turn, are coordinated by an array of physiologic rhythms generated by the suprachiasmatic nuclei, a circadian pacemaker in the hypothalamus.¹³⁻¹⁵ The circadian timing system encompasses these molecular, cellular, and physiologic components and generates 24-hour rhythms in anticancer drug metabolism and cellular proliferation.^{13,15,16} The circadian timing system in cancer patients has been assessed with continuous rest-activity monitoring using a wrist actigraph, which detected circadian disruption in approximately 1 in 3 cancer patients.^{17,18} In a previous work, baseline circadian disruption was associated robustly with fatigue and appetite loss in 251 patients with metastatic colorectal cancer.¹⁷⁻¹⁹ Fatigue and appetite loss also were observed in individuals who were suffering from jet lag or who were engaged in shift work—2 conditions that disrupt the circadian timing system.^{20,21} Moreover, fatigue and body weight loss, objective yet unspecific measures of appetite loss, occurred more frequently in cancer patients who had circadian alterations on chemotherapy.²² Body weight loss also was associated with decreased physical activity in patients undergoing actigraphy monitoring.²³ For the current investigation, we hypothesized that early onset fatigue and/or weight loss reflect chemotherapy-induced circadian disruption, a condition that interferes selectively with the efficacy of chronomodulated chemotherapy. To probe this hypothesis, we performed a post hoc analysis of data prospectively collected for an international, randomized, phase 3 trial (European Organization for Research and Treatment of Cancer [EORTC] 05963) that was conducted in 564

chemotherapy-naive patients with metastatic colorectal cancer who were randomized to receive first-line chemotherapy with either chronoFLO4 or FOLFOX2.¹¹

MATERIALS AND METHODS

Study Objectives

For the current study, we examined the primary hypothesis that early onset fatigue and body weight loss, occurring during the initial 4 weeks of treatment, selectively indicate a poor prognosis for the survival of patients who are receiving a fixed chronotherapy schedule for metastatic colorectal cancer. This symptom cluster was selected as being related to the occurrence of circadian disruption in cancer patients who are receiving chemotherapy.¹⁰ Secondary objectives included the prognostic relevance of other main, severe toxicities that have no known association with circadian disruption.^{10,17-19}

Study Population and Chemotherapy Schedules

Patients with chemotherapy-naive, metastatic colorectal cancer were enrolled in the EORTC 05963 trial between October 1998 and February 2002.¹¹ They provided written informed consent and were randomized to receive first-line chemotherapy with combined fluorouracil, leucovorin, and oxaliplatin either as a chronomodulated infusion (chronoFLO4) or with a conventional, non time-stipulated schedule (FOLFOX2). Details of these schedules have been described elsewhere.¹¹

Study Population and Toxicity Evaluation

The landmark population in this study involved patients who received at least 2 courses of chemotherapy according to EORTC 05963. This time span covered the initial 4 weeks on chemotherapy. Clinical and hematologic toxicities were graded after each treatment course according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Fatigue and appetite loss were rated by the physician. Whereas chemotherapy-induced fatigue was reported after each course, appetite loss was not systematically assessed. However, body weight was measured systematically before each chemotherapy course and was chosen as a surrogate quantitative indicator of decreased appetite. We considered toxicity clinically meaningful if the patient experienced either grade ≥ 2 fatigue or weight loss $\geq 5\%$ of baseline body weight over the initial 2 courses of chemotherapy. The clinical relevance of the cutoff values selected a priori for our study has been described elsewhere.^{8,22,24}

The following toxicities were not considered to be associated with circadian disruption: diarrhea, stomatitis,

mucositis, hand-foot syndrome, peripheral sensory neuropathy, nausea, vomiting, leukopenia, neutropenia, anemia, and thrombocytopenia. To distinguish the respective impact of each type of toxicity, patients in each treatment group were categorized into 4 subgroups according to the occurrence of no toxicity (subgroup 1), fatigue-weight loss only (subgroup 2), fatigue-weight loss associated with other grade ≥ 3 toxic events (subgroup 3), or other grade ≥ 3 toxicities only (subgroup 4).

Statistical Methods

The primary endpoint of the current study was the association between toxicity and OS, defined as the time between the end (day 14) of the second treatment course and the date of death irrespective of cause. Patients who remained alive at the time the database was locked or who were lost to follow-up were censored on the date of last information on vital status. At that date, after a median follow-up of 87 months (range, 68-108 months), 488 events had occurred (89.9%).

The proportions of patients in each toxicity subgroup were computed for each treatment modality. The rates were compared with a 2-sided chi-square test. Actual dose intensities (per square meter per week) received in the first 2 courses of chemotherapy and throughout the whole treatment span were compared between the 4 patient categories with the nonparametric Mann-Whitney *U* test. The survival functions of the 4 subgroups, as defined by the occurrence of fatigue-weight loss and/or other toxicities after the initial 2 treatment courses, were estimated using the Kaplan-Meier method and were compared using a log-rank test separately in each treatment arm. The hazard ratio (HR) of an earlier death associated with the occurrence of toxicity was estimated using Cox proportional hazards models separately in each treatment arm. Multivariate prognostic models for OS included other parameters that were force-entered, whereas toxicity category was conditionally added. In the first step, parameters that predicted the occurrence of any clinically relevant toxicity (fatigue-weight loss and/or other toxicities) were identified with a thorough screening of clinical features using a binary logistic univariate regression model. The characteristics included sex, age, baseline body mass index, World Health Organization performance status at inclusion, the number of metastatic sites, the percentage of liver involvement by tumor, dose intensities of 5-fluorouracil and oxaliplatin over the first 2 cycles, previous adjuvant chemotherapy, Duke stage at diagnosis, primary tumor site, surgical resection of the primary tumor, previous surgery for metastases, baseline leukocyte count, and

baseline alkaline phosphatase level. Upon verification of the absence of collinearity ($r \leq 0.37$), these parameters were added in a block to the prognostic model. For the second step, the subgroup category according to toxicity occurrence was added to the multivariate model. The same statistical procedure was performed to examine the independent predictive role of chemotherapy-induced toxicity on the time to progression (TTP), which was calculated from the end of the second course until documented disease progression, death, or last contact, whichever occurred first. A similar multivariate Cox hazard regression model was performed separately using the occurrence of fatigue-weight loss and the occurrence of other toxicities as covariates to validate the specificity of either toxicity on TTP and OS for each treatment modality. Further sensitivity analyses were performed excluding patients with missing data. Because 2 independent models were fitted for FOLFOX2 and chronoFLO4 modalities, the threshold for statistically significant differences was set at $P \leq .025$ according to a Bonferroni correction. The rate of missing data per item for the parameters considered (blood counts, clinical toxicities, and body weight) after the first 2 courses of chemotherapy was of 1.3%. Sensitivity analyses performed that eliminated patients who had at least 1 missing item yielded results that were strictly comparable to those reported in the main landmark group (data not reported). All analyses were performed using PASW Statistics 18 software (SPSS Inc., Chicago, Ill).

Study Population

Of 564 enrolled and randomized patients in the EORTC 05963 trial, 543 patients (96.3%) received at least 2 courses of chemotherapy and constituted the study population (Fig. 1). The clinical and demographic features of the 272 patients who received FOLFOX2 and the 271 patients who received chronoFLO4 are presented according to the occurrence of fatigue-body weight loss and other toxicities (data not shown).

RESULTS

Dose Intensities and Toxicities

The actual dose intensities of 5-fluorouracil and oxaliplatin over the initial 2 treatment courses varied according to the toxicity category in the FOLFOX2 schedule ($P = .008$ and $P = .001$, respectively), but not in the chronoFLO4 schedule ($P = .24$ and $P = .20$, respectively). Fatigue-weight loss was encountered in 73 patients (26.8%) in the FOLFOX2 group and 69 patients (25.5%) in the chronoFLO4 group ($P = .72$), whereas other toxicities occurred in 40 patients (14.7%) and 54

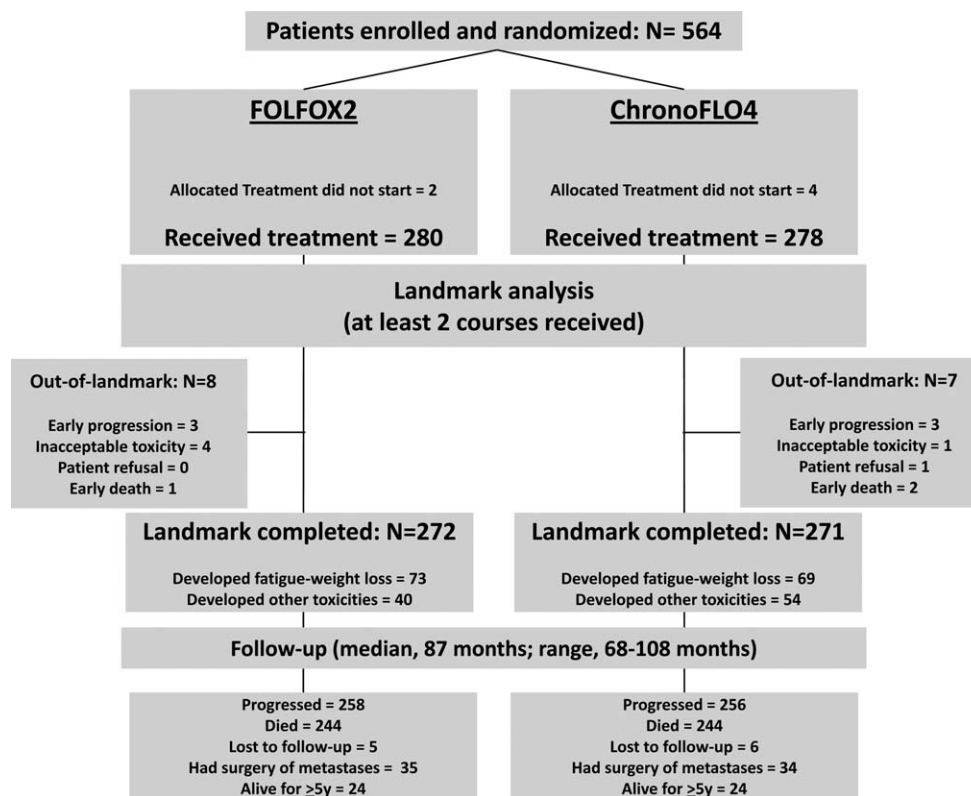


Figure 1. This is a flow chart of the 564 patients who were enrolled and randomized on the European Organization for Research and Treatment of Cancer 05963 trial. FOLFOX2 indicates combined 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule; chronoFLO4 indicates combined, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule.

patients (19.9%), respectively ($P = .11$) (Fig. 2). The co-occurrence of fatigue-weight loss and other toxicities was significantly more frequent in the chronoFLO4 group ($n = 27$; 10.0%) than in the FOLFOX2 group ($n = 14$; 5.1%; $P = .036$). The relative proportions of patients in each of the 4 toxicity categories did not differ according to treatment modality with statistical significance ($P = .07$) (Fig. 2). Women who received chronoFLO4 were significantly more likely to develop toxicity than men who received chronoFLO4 ($P = .003$) (Table 1). Patients with good baseline performance status displayed a significantly reduced risk of experiencing toxicity after either treatment schedule (Table 1). The regimen and dosing of supportive medications, including steroids, were similar in both treatment arms.¹¹

Tumor Response and Progression-Free Survival

Objective response rates were similar in the 4 toxicity categories for patients in the FOLFOX2 group ($P = .80$) (Table 2). Conversely, an objective response was achieved in 22.2% of patients with fatigue-weight loss and other

toxicities on chronoFLO4 compared with from 40.5% up to 51.9% of patients in the other toxicity subgroups ($P = .06$) (Table 2).

The 4 toxicity categories displayed similar curves for TTP for patients who received FOLFOX2 (log-rank test; $P = .11$) (Fig. 3A). Conversely, a significant difference in TTP was observed according to toxicity category among the patients who received chronoFLO4 (log-rank test; $P < .0001$). The patients with fatigue-weight loss displayed the worst outcome, irrespective of the association of this symptom cluster with other toxicities (Fig. 3B). This translated into a higher risk of earlier progression on chronoFLO4 for patients with fatigue-weight loss, either alone ($P < .0001$) or combined with other toxicities ($P = .001$). No such relation was observed among patients who had toxicities other than fatigue-weight loss ($P = .59$). Fatigue-weight loss was confirmed as an independent prognostic indicator of the risk of earlier progression on chronoFLO4 using the multivariate Cox model ($P < .001$). No such correlation was validated for the patients who had toxicities other than fatigue-weight loss

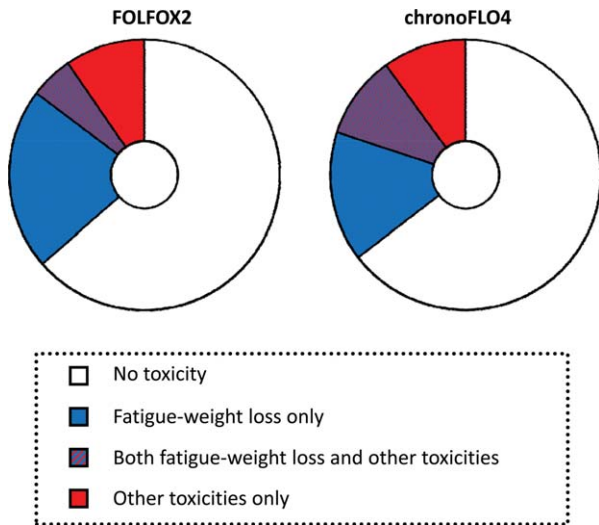


Figure 2. Relative proportions of patients without toxicity (group 1; white), with fatigue-weight loss only (group 2; blue), with both fatigue-weight loss and other toxicities (group 3; blue and red stripes), and with other toxicities only (group 4; red) are illustrated for each treatment arm. FOLFOX2 indicates combined 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule; chronoFLO4, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule.

($P = .54$) (Table 3). The multivariate models further confirmed the lack of predictive value of any toxicity category for TTP in the patients who received FOLFOX2 (Table 3). In summary, the occurrence of fatigue-weight loss was not related significantly to TTP in the FOLFOX2 group ($P = .07$) (Fig. 3C), whereas it was strongly associated with a shorter TTP in the chronoFLO4 group ($P < .0001$) (Fig. 3D).

Prognostic Value of Toxicity in Overall Survival

OS curves were similar in the 4 toxicity categories for patients in the FOLFOX2 group (log-rank test; $P = .45$) (Fig. 4A), with similar median survival duration ranging from 16.4 to 19.8 months (Table 2). However, the survival of patients in the chronoFLO4 group differed significantly as a function of toxicity category (log-rank test; $P < .0001$), with median values ranging from 13.7 months (fatigue-weight loss category) to 21.6 months (no clinical toxicity category) (Table 2, Fig. 4B). Patients with fatigue-weight loss in the chronoFLO4 group displayed an increased risk of earlier death (fatigue-weight loss only, $P = .002$; fatigue-weight loss combined with other toxicities, $P < .0001$) compared with patients without

TABLE 1. Univariate Binary Logistic Regression for the Identification of the Parameters Potentially Predictive for the Occurrence of Any Toxicity (Fatigue-Weight Loss, Other, or Both) Separately in Each Treatment Arm^a

Variable	Toxicity Occurrence			
	FOLFOX2		ChronoFLO4	
	OR (95% CI)	P	OR (95% CI)	P
Sex				
Men		NS	1.00	.003
Women			2.19 (1.32-3.65)	
Baseline WHO PS				
0	1.00	.006	1.00	.028
1	1.29 (0.76-2.19)		1.44 (0.84-2.47)	
2	4.48 (1.78-11.27)		2.94 (1.32-6.56)	
No. of metastatic sites				
1	1.00	.05		NS
2	0.94 (0.52-1.68)			
≥3	1.97 (1.05-3.68)			
Quantitative dose intensity				
I-OHP, mg/m ² /wk	NS		0.96 (0.92-0.998)	.038
5-FU, g/m ² /wk	0.11 (0.02-0.55)	.007	0.15 (0.04-0.56)	.004

Abbreviations: 5-FU, 5-fluorouracil; ChronoFLO4, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule; CI, confidence interval; FOLFOX2, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule; I-OHP, oxaliplatin; NS, nonsignificant; OR, odds ratio; WHO PS, World Health Organization performance status.

^aThe complete list of parameters accounted for is provided in the text (see Materials and Methods). The parameters that were not significant in any model are not listed here.

TABLE 2. Clinical Outcomes (Objective Response Rate, Time to Progression, and Overall Survival) According to Toxicity Category Separately in Each Treatment Arm

Treatment Arm	Outcome		
	ORR (95% CI), %	Median TTP (95% CI), mo	Median OS (95% CI), mo
FOLFOX2			
Group 1, n = 175 ^a	48 (40.6-55.40)	9.1 (8.0-10.2)	19.8 (17.7-22.0)
Group 2, n = 42	40.7 (25.8-55.6)	6.1 (3.4-8.9)	17.1 (12.2-22.0)
Group 3, n = 27	42.9 (24.2-61.6)	5.6 (3.0-8.2)	16.4 (7.2-25.6)
Group 4, n = 27	42.2 (23.6-60.8)	8.5 (6.1-10.9)	19.6 (15.7-23.4)
All, n = 271	46 (40.1-51.9)	8.7 (7.9-9.4)	18.6 (17.0-20.1)
ChronoFLO4			
Group 1, n = 173	48.6 (41.2-56.1)	9.4 (8.5-10.4)	21.6 (19.2-24.0)
Group 2, n = 59	40.5 (28-53)	6.0 (3.9-8.2)	13.7 (8.8-18.6)
Group 3, n = 14	22.2 (0.5-44)	5.6 (3.1-8.2)	13.9 (8.6-19.2)
Group 4, n = 26	51.9 (32.7-71.1)	10.2 (5.8-14.6)	19.1 (12.6-25.7)
All, n = 272	45 (39.1-50.9)	8.4 (7.4-9.3)	19.7 (18.4-21.0)

Abbreviations: ChronoFLO4, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule; CI, confidence interval; FOLFOX2, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule; ORR, objective response rate; OS, overall survival; TTP, time to progression.

^aGroup 1: no toxicity; 2: fatigue-weight loss only; 3: both fatigue-weight loss and other toxicities; 4: other toxicities only.

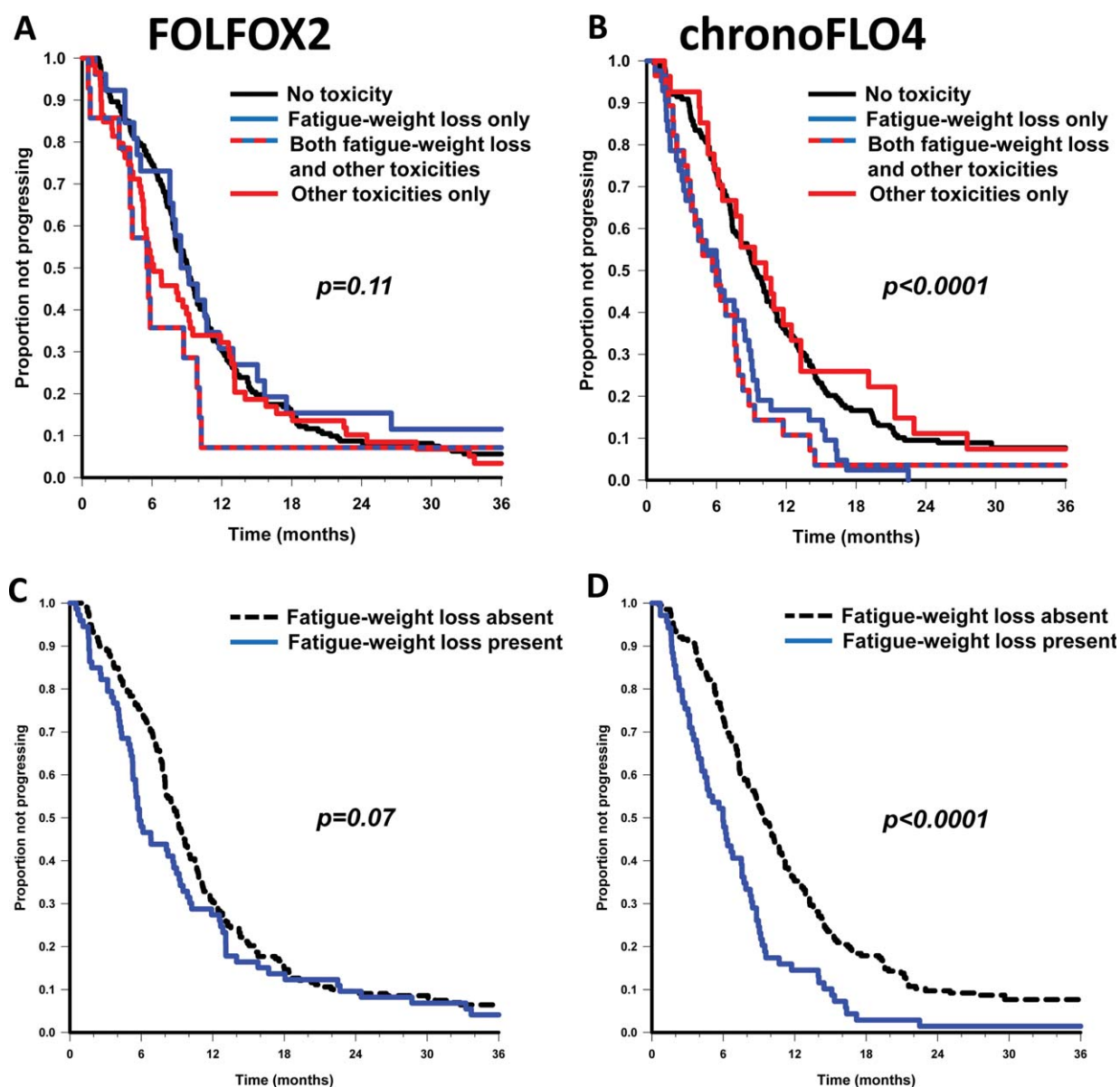


Figure 3. These Kaplan-Meier curves depict the time to progression in each treatment arm: (A,C) combined 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule (FOLFOX2) and (B,D) 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule (chronoFLO4). (A,B) Curves illustrate the time to progression for the 4 patient groups categorized according to the occurrence of no toxicity (group 1; solid black lines), fatigue-weight loss only (group 2; solid blue lines), both fatigue-weight loss and other toxicities (group 3; dashed blue and red lines), and other toxicities only (group 4; solid red lines). (C,D) Curves illustrate the time to progression for the 4 patient groups categorized according to the occurrence of fatigue-weight loss (groups 2 and 3; solid blue lines) and the absence of fatigue-weight loss (groups 1 and 4; dashed black lines). P values were calculated with the log-rank test.

any toxicity in this group. No difference in survival was observed between among patients who received chronoFLO4 according to toxicities other than fatigue-weight loss ($P = .37$).

The increased risk of earlier death associated with fatigue-weight loss on chronoFLO4, either alone ($P = .009$) or combined with other toxicities ($P = .006$),

remained significant, independent of the other known prognostic factors and parameters associated with these toxicities in a multivariate Cox model (Table 3). The models confirmed the lack of prognostic value for toxicities other than fatigue-weight loss in the chronoFLO4 group and for any toxicity category in the FOLFOX2 group (Table 3).

TABLE 3. Variables Included in the Multivariate Cox Proportional Hazard Models for Time to Progression and Overall Survival Separately in Each Treatment Arm

Variable	Time to Progression				Overall Survival			
	FOLFOX2		ChronoFLO4		FOLFOX2		ChronoFLO4	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Sex								
Men		NS	1.00	.012	1.00	.001	1.00	.013
Women			1.42 (1.08-1.87)		0.61 (0.46-0.82)		1.43 (1.08-1.89)	
Baseline WHO PS								
0	1.00	<.0001		NS	1.00	<.0001		NS
1	1.49 (1.12-1.97)				1.51 (1.13-2.01)			
2	2.82 (1.67-4.75)				4.43 (2.53-7.76)			
No. of metastatic sites								
1		NS		NS	1.00	<.0005		NS
2					1.17 (0.85-1.60)			
≥3					1.81 (1.23-2.62)			
Baseline ALP, IU/L								
≤300	1.00	.002		NS	1.00	<.0001		NS
>300	1.74 (1.25-2.49)				2.02 (1.44-2.83)			
Unknown	1.67 (0.83-3.39)				1.31 (0.64-2.70)			
Toxicity group								
1) No toxicity		NS	1.00	.002		NS	1.00	.006
2) Fatigue-weight loss only			1.80 (1.23-2.67)				1.65 (1.13-2.39)	
3) Both fatigue-weight loss and other toxicities			1.82 (1.14-2.92)				1.92 (1.20-3.05)	
4) Other toxicities only			0.87 (0.55-1.37)				1.30 (0.82-2.07)	

Abbreviations: ALP, alkaline phosphatase; ChronoFLO4, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule; CI, confidence interval; FOLFOX2, 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule; HR, hazard ratio; NS, nonsignificant; WHO PS, World Health Organization performance status.

In aggregate, OS was not influenced by the occurrence of fatigue-weight loss ($P = .12$) (Fig. 4C) or other toxicities ($P = .89$; results not shown) for patients in the FOLFOX2 group. Conversely, a higher risk of earlier death resulted from the occurrence of fatigue-weight loss (Fig. 4D) ($P < .0001$) and other toxicities ($P = .022$; results not shown) in the chronoFLO4 group. The multivariate Cox model ruled out other clinical toxicities as predictors of OS ($P = .08$; results not shown). However, the fatigue-weight loss cluster remained a statistically significant predictor of poor survival in this analysis ($P = .001$).

DISCUSSION

This study revealed that the advent of fatigue or weight loss during the initial 4 weeks on chemotherapy predicted poor progression-free survival and OS on a fixed chronotherapy schedule in patients with metastatic colorectal cancer. No such relation was observed between these symptoms and efficacy outcomes in patients who received conventional chemotherapy. The current study also demonstrated no predictive value of other severe clinical toxicities for any efficacy outcome regardless of the delivery schedule. Thus, the current report constitutes the first clinical proof of a negative relation between toxicity and both TTP and survival in

oncology. Prior studies consistently reported a positive association between specific toxicities and clinical outcomes in patients who received various chemotherapies for many kinds of malignancies.²⁻⁹ The specificity of the current finding for chronotherapy delivery supports a shared circadian biologic mechanism correlating poor anticancer activity with poor tolerability.¹³ Fatigue-weight loss was highlighted here as a critical symptom cluster that may impair the efficacy of chronotherapy. Fatigue, anorexia, and body weight loss are frequent chemotherapy-induced complaints that often cluster and may share common mechanisms.^{19,22,25-28} Prior studies supported the hypothesis that the fatigue-weight loss symptom cluster would result from circadian disruption.^{19,22} Therefore, we chose the occurrence of this cluster of systemic toxicity as an indirect surrogate for chemotherapy-induced circadian disruption.

In the current work, no difference in overall toxicity rates during the initial 2 courses of treatment was observed as a function of treatment schedule (Fig. 2). However, early toxicities on chronoFLO4 were almost twice as frequent in women compared with men. Hence, the higher toxicity incidence in women may have been particularly detrimental for the efficacy of chronomodulated chemotherapy, which is based biologically on a coordinated,

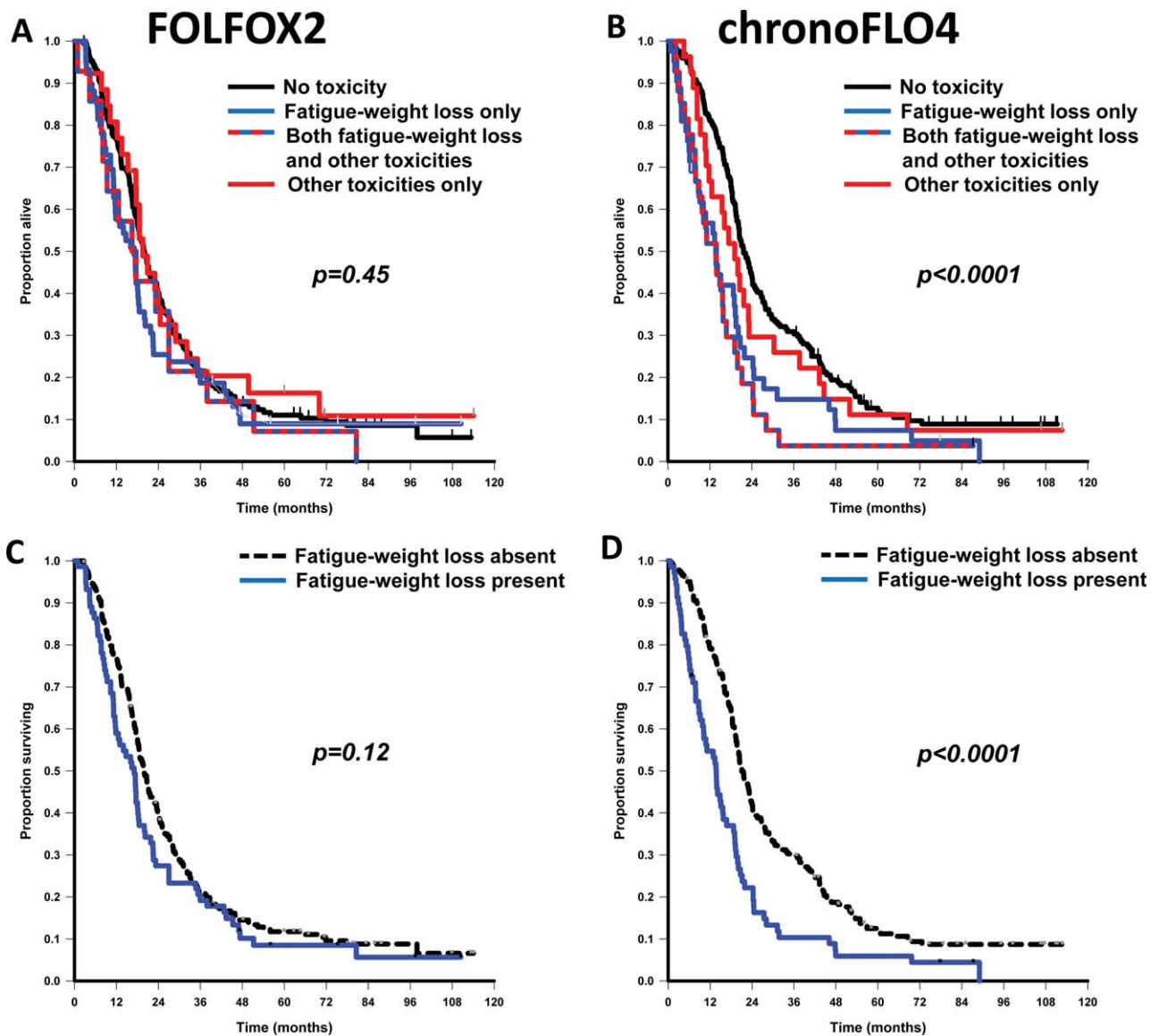


Figure 4. These Kaplan-Meier curves depict overall survival in each treatment arm: (A,C) combined 5-fluorouracil, leucovorin, and oxaliplatin delivered on a conventional schedule (FOLFOX2) and (B,D) 5-fluorouracil, leucovorin, and oxaliplatin delivered on a circadian-based, chronomodulated schedule (chronoFLO4). (A,B) Curves illustrate survival for the 4 patient groups categorized according to the occurrence of no toxicity (group 1; solid black lines), fatigue-weight loss only (group 2; solid blue lines), both fatigue-weight loss and other toxicities (group 3; dashed blue and red lines), and other toxicities only (group 4; solid red lines). (C,D) Curves illustrate survival for the 4 patient groups categorized according to the occurrence of fatigue-weight loss (groups 2 and 3; solid blue lines) and the absence of fatigue-weight loss (groups 1 and 4; dashed black lines). P values were calculated with the log-rank test.

functional biologic clock.^{13-16,29} Thus, wrongly dosed or poorly timed circadian chemotherapy could disrupt both the central pacemaker and the peripheral oscillators, resulting in symptoms of circadian disruption (fatigue, anorexia, weight loss) and toxic effects in peripheral tissues, which are equipped with functional molecular clocks.^{16,30,31}

The current findings indicate that chemotherapy-induced circadian disruption, as estimated here with the occurrence of fatigue or weight loss, may be detrimental for the efficacy of circadian-based chemotherapy. This is not the case, however, for conventional chemotherapy, in which the timing of administration varies both between and within patients.¹³

Two main limitations of the current study should be acknowledged. First, patients were not randomized to develop toxicity. Therefore, it may be argued that other factors associated with fatigue-weight loss or other toxicities would be the main determinants of the survival differences observed, and toxic events would merely form a surrogate marker of a poor prognosis related to other determinants. To rule out this possibility, we systematically proceeded with a thorough screening of all parameters that possibly might account for the induction of either toxicity. All factors were forcibly added to the Cox survival model, whereas the toxicity subgroup category was added conditionally to the model to explore whether it had independent prognostic value above and beyond the other parameters considered. Indeed, the occurrence of chemotherapy-induced fatigue-weight loss remained an independent prognostic factor for both TTP and OS in the chronoflora group despite the adjustment for the other parameters and known prognostic factors. This analysis confirmed the prognostic relevance of sex for chronotherapy¹² along with the relevance of PS and alkaline phosphatase for conventional chemotherapy^{32,33} (Table 3). Second, the grading of fatigue is subjective, with uncertain reliability and reproducibility. However, in 2 large meta-analyses that included individual data reporting subjective parameters, PS or patient self-estimated quality-of-life measures at baseline independently predicted OS.^{33,34} Thus, pertinent subjective parameters added relevant prognostic information to that derived from objective measures.

Furthermore, circadian function can be quantified both noninvasively and objectively in cancer patients using wrist actimetry monitoring.^{17,18,35} The early detection of circadian disruption indeed may readily help its minimization through the modification of drug doses and/or timing administration, resulting in personalized rather than fixed chronotherapy schedules.

In conclusion, the patients who displayed fatigue-weight loss within the initial 4 weeks of a fixed chronotherapy schedule were less likely to benefit from it. This finding provides a clinically relevant tool for further treatment optimization, which also may benefit from a quantitative dynamic approach based on circadian rhythm monitoring. A main implication of the current study, which deserves prospective validation, is that circadian-based schedules should achieve low toxicity to optimize efficacy, a finding that also has been supported experimentally.¹³ This paradigm seems to be specific for chronotherapy. It contrasts with the current concept of

conventional chemotherapy, in which the maximum tolerated dose of an anticancer drug represents the optimal therapeutic dose.

FUNDING SUPPORT

The current study was supported by the Association Internationale pour la Recherche sur le Temps Biologique et la Chronothérapie (ARTBC International).

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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