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SEX MODERATES CIRCADIAN CHEMOTHERAPY EFFECTS ON SURVIVAL OF PATIENTS WITH METASTATIC COLORECTAL CANCER: A META-ANALYSIS

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ABSTRACT

Background Molecular circadian clocks can modify cancer chemotherapy effects, with a possible moderation according to sex differences. We investigated whether sex determine the optimal delivery schedule of chemotherapy for metastatic colorectal cancer.

Patients and methods A meta-analysis was performed using individual data from three international Phase III trials comparing 5-fluorouracil, leucovorin and oxaliplatin administered in chronomodulated (chronoFLO) or conventional (CONV) infusions. The data from 345 females and 497 males were updated at 9 years. The main end point was survival.

Results Overall survival was improved in males on chronoFLO when compared with CONV (P = 0.009), with respective median values of 20.8 (95% CL, 18.7 to 22.9) and 17.5 months (16.1 to 18.8). Conversely, median survival was 16.6 months (13.9 to 19.3) on chronoFLO and 18.4 months (16.6 to 20.2) on CONV in females (P = 0.012). The sex versus schedule interaction was a strong predictive factor of optimal treatment schedule, with a hazard ratio of 1.59 (1.30 to 1.75) for overall survival (P = 0.002) in multivariate analysis.

Conclusions Males lived significantly longer on chronomodulated chemotherapy rather than on conventional chemotherapy. The current chronoFLO schedule deserves prospective assessment as a safe and more effective first-line treatment option than conventional delivery for male patients.

Key words: chronotherapy, colorectal cancer, drug delivery, FOLFOX, gender, meta-analysis

INTRODUCTION

The circadian timing system consists of a network of endogenous molecular clocks which generate about 24-h oscillations in each cell and are coordinated by a hypothalamic pacemaker. The circadian timing system gates cell division, thereby regulating apoptosis and DNA repair as well as several signaling and metabolic pathways relevant for cancer processes and their treatments. The molecular clock involves the interplay of 15 clock genes, which rhythmically control clock proteins and promoter regions of critical genes for cell cycle and drug bioactivation, detoxification and/or targets [1, 2]. Molecular clocks are effectively coordinated through an array of physiological rhythms such as rest-activity, core body temperature, hormonal secretion and sympathetic/parasympathetic tone, which are synchronized by the hypothalamic pacemaker. Both experimental and clinical evidence support an important role for circadian disruption in carcinogenesis and cancer progression, while circadian rhythm regulation enhances cancer inhibition [3–5]. Circadian timing of chemotherapy administration modifies its tolerability 2- to 10-fold, as shown for 40 anticancer drugs in experimental models. Strikingly, optimal antitumor efficacy usually results from drug delivery at the circadian stage when it achieves best tolerability and least disruption of the circadian timing system [1]. The mechanisms responsible for this observation involve circadian changes in enzymatic activities and/or gene expression responsible for drug transport, bioactivation, detoxification and pharmacodynamics [1, 6]. More specifically, several key rhythmic determinants of 5-fluorouracil (5-FU) and oxaliplatin tolerability peak 12 h apart both in nocturnally active rodents and in diurnally active humans. These findings led to test the effectiveness of chronomodulated chemotherapy, in an attempt to improve the outcome and to reduce toxicity in cancer patients. Phase I, II and III clinical trials tested the circadian timing hypothesis in patients with metastatic colorectal cancer [1]. Three international randomized Phase III trials assessed whether the combination of first-line 5-FU–leucovorin (5-FU-LV) and oxaliplatin would benefit from a chronomodulated administration (chronoFLO), when compared with conventional delivery (CONV), either as a constant rate flat infusion (flatFLO) or as FOLFOX2 [7–9]. In the first two trials, chronoFLO significantly improved the objective response (ORR) rate, when compared with CONV [7, 8]. The prolongation of survival was found in the first but not in the subsequent two studies [7–9]. An exploratory analysis of the third trial data revealed that chronoFLO significantly improved survival when compared with FOLFOX in males, while an opposite effect was found in females [9]. The sex versus schedule interaction was statistically validated in multivariate analyses for both progression-free survival (PFS) and overall survival (OS) in this trial [9]. This finding led us to hypothesize that male and female patients with metastatic colorectal cancer responded differently to the circadian timing of 5-FU-LV and oxaliplatin-based therapy. It is noteworthy that male mice were used for most of the preclinical chronotherapeutic studies of 5-FU and oxaliplatin that were the basis for the chronomodulated schedule used in subsequent clinical trials [1]. Moreover, male patients were mainly involved in the human translational studies that supported the concept of 5-FU and oxaliplatin chronomodulation [1, 10].

Here we update the individual data of the patients included in the three aforementioned international Phase III trials involving chronotherapy. We perform a meta-analysis in order to establish whether sex is a critical determinant of the optimal schedule of the reference three-drug chemotherapy against colorectal cancer.

PATIENTS AND METHODS

STUDY DESIGN

ChronoFLO involved chronomodulated infusions of 5-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. In the first two trials (T1 and T2), patients were randomly assigned to receive either chronoFLO or a flat infusion of the same three drugs (CONV) over 5 days every 3 weeks [7, 8]. In the third trial (T3), patients received either chronoFLO over 4 days or FOLFOX2 every 2 weeks [9]. FOLFOX2 consisted of oxaliplatin and LV as a 2-h infusion on day 1 and LV only on day 2, starting between 0900 and 1600 h. The FU infusion was delivered at a constant rate for 22 h on days 1 and 2 [9]. In T3, intra-patient dose escalation was planned in both arms for 5-FU, in order to treat each patient near individual maximum dose intensity.

The meta-analysis was conducted using all individual patient data. Dates of progression and death were verified and updated for each patient. Follow-up was terminated at 9 years after inclusion of the first patient in each trial.

STATISTICAL METHODS

Individual data of all randomly assigned patients were included in the pooled analysis. OS was defined as the time from the date of randomization to the date of death from any cause. Forty-seven patients (5.5%) lost to follow-up before 9 years were censored on the date of their last visit, without any imbalance according to sex or schedule.

PFS was defined as the time from randomization to progression or death whichever came first. Patients lost to follow-up or those with no date of progression recorded were considered as progression-free and censored at the date of last follow-up. ORR was assessed every third or fourth treatment course according to trial specification, and defined according to WHO criteria.

The Kaplan–Meier survival curves were plotted and log-rank tests were performed to compare survival on chronoFLO and CONV, in the whole population and separately in males and females. Response rates were compared according to schedule and sex using two-sided $\chi 2$ test. The hazard ratios (HRs) of an earlier death were represented for each variable and treatment schedule using Forrest plots. For PFS and OS, the relative benefit of treatment was explored using a trial-stratified Cox proportional hazard regression model, with a forward selection procedure. Logistic regression was used to explain differences in response rates, using a model with a trial-specific intercept. Homogeneity between trials regarding the interaction between sex and treatment was investigated using Cochran's Q statistics, by testing the equality of the HRs for PFS and OS and of the odds ratios for the response rate. Candidate prognostic and predictive factors of OS, PFS and response were selected for multivariate analyses, based on statistical validation with $P = 0.10$ in univariate analysis. The effects of sex, schedule and their interaction were adjusted for each clinical prognostic factor selected upon univariate analysis. The final model included treatment schedule and sex with other factors added through a forward selection procedure. The 95% confidence intervals of HRs for sex versus treatment interaction and other prognostic factors were computed in the Cox models. The 95% confidence intervals of odds ratios (OR) for sex versus treatment interaction and other prognostic factors were also computed in the logistic regression. All tests were two-sided. P-values <0.05 were considered as statistically significant. All analyses were performed using SPSS 16.0. Forrest plots were drawn using R 2.12.2. The current report abides by the guidelines of the PRISMA statement [11].

RESULTS

PATIENT CHARACTERISTICS

From 1990 to 2003, 842 patients with metastatic colorectal cancer (345 females and 497 males), were registered in one of three multicenter randomized trials, each one involving 8 to 36 centers in 3 to 10 countries. Overall, chronoFLO was administered to 180 female and 240 male patients, while CONV was given to 165 female and 257 male patients. The main clinical characteristics were similar in male and female patients on each treatment schedule, despite minor and non-significant imbalances (Table 1). Patients received a median of 9 courses (range: 1 to 49) of protocol treatment. The median follow-up was 93 months (67 to 108). Second-line treatment consisted of cross-over from flat to chronomodulated infusion in 24% of the patients registered in Trials 1 or 2. In the third trial, 70.6% of the patients received second-line chemotherapy, consisting of irinotecan for ≈56% in each arm. No patient received any targeted therapy unless recurrence occurred after 2005, i.e. 3 years after inclusion of the last patient. Secondary metastases resection was performed in 141 patients (16.7%). The updated results of each trial revealed consistent improvements for all three efficacy end points in males on chronoFLO when compared with CONV. In contrast, females displayed inconsistent benefit from CONV versus chronoFLO across the three trials (supplementary material S1, available at Annals of Oncology online).

842 patients	Female		Male	
Characteristics	Conv (%)	ChronoFLO (%)	Conv (%)	ChronoFLO (%)
No. of patients	165 (19.5)	180 (21)	257 (30.5)	240 (28.5)
Median age	60 (50–68)	59 (51–67)	62 (54–68)	62 (54–67)
Colon	126 (76)	141 (78.3)	183 (71.2)	173 (72.1)
Rectum	39 (24)	39 (21.7)	74 (28.8)	67 (27.9)
Performance status				
0	69 (41.8)	80 (44.4)	134 (52.1)	122 (50.8)
1	75 (45.5)	78 (43.3)	102 (39.7)	90 (37.5)
2	21 (12.7)	22 (12.2)	21 (8.2)	28 (11.7)
Synchronous metastases	102 (61.8)	113 (62.8)	180 (70.0)	162 (67.5)
No. of meta. sites				
1 (%)	93 (56.4)	93 (51.7)	136 (52.9)	128 (53.3)
2 (%)	48 (29.1)	67 (37.2)	84 (32.7)	81 (33.8)
≥3 (%)	24 (14.5)	20 (11.1)	37 (14.4)	31 (12.9)
Liver (%)	139 (84.2)	152 (84.4)	218 (84.8)	205 (85.4)
Lung (%)	55 (33.3)	66 (36.7)	95 (37)	87 (36.2)
Liver involvement				
<25%	72 (51.8)	85 (55.9)	111 (50.9)	120 (58.5)
≥25%	67 (48.2)	65 (42.8)	103 (47.2)	81 (39.5)
Unknown	0	2 (1.3)	4 (1.8)	4 (2.0)
Adjuvant chemo. (%)	30 (18.2)	31 (17.2)	32 (12.5)	41 (17.1)
CEA (ng/ml)				
≤10 (%)	38 (23)	50 (27.8)	69 (26.8)	62 (25.8)

Table 1. Characteristics of the 842 patients included in the three randomized international trials

ASSOCIATION BETWEEN ANTITUMOR EFFICACY, TREATMENT SCHEDULE AND GENDER

Irrespective of sex, OS was similar for both treatment schedules, the median being 18.7 months (17.2 to 20.1) on chronoFLO and 17.6 months (16.6 to 18.6) on CONV (log-rank P = 0.66). PFS did not differ between patients on chronoFLO or CONV, the median being 8.6 months (7.9 to 9.3) and 8.1 months (7.4 to 8.9), respectively (log-rank P = 0.92). The ORR rate was 46% on chronoFLO and 39.8% on CONV (P = 0.07).

Interactions between sex and treatment schedule were investigated using multivariate Cox models for each survival end point, and a multivariate logistic model for the response rate. No other interaction was introduced in the multivariate model, since no differential treatment effect was found in each category of any other clinical factor. The final models showed that sex × *treatment interaction significantly modified OS, PFS and response rate. Thus, regarding OS, the HR of chronoFLO4 relative to CONV was 1.32 in females (P = 0.018), while this HR was 0.63 in males (P = 0.002). Similar figures were found for the HR corresponding to PFS and, to a lesser extent, for the odds ratio related to the response rate (Table 2). Other factors found to be significantly prognostic included performance status, number of metastatic sites and percent liver invasion by tumor. This latter factor was only prognostic for OS (Table 2).

Prognostic factor	Hazard ratio	IC 95%	*P*
Overall survival			
Gender (M versus F)	1.12	0.95–1.45	0.13
Schedule (chrono versus conv)	1.32	1.05–1.65	0.016
Gender × schedule	0.63	0.47–0.85	0.002
Performance status (1 and 2 versus 0)	1.51	1.30–1.75	<0.001
No. of sites			
2 versus 1	1.70	1.45–2.00	<0.001
>2 versus 1	1.90	1.52–2.37	<0.001
Percent liver involvement			
<25% versus none	0.75	0.61–0.93	0.009
≥25% versus none	1.25	1.01–1.55	0.044
Progression-free survival			
Gender (M versus F)	1.03	0.84–1.27	0.75
Schedule (chrono versus conv)	1.23	0.99–1.53	0.061
Gender × schedule	0.72	0.54–0.95	0.021

Prognostic factor	Hazard ratio	IC 95%	*P*
Performance status (1 and 2 versus 0)	1.45	1.25–1.68	<0.001
No. of sites			
2 versus 1	1.72	1.42–2.08	<0.001
>2 versus 1	2.38	1.84–3.09	<0.001
Lung metastases	0.80	0.66–0.97	0.025
Percent liver involvement			
<25% versus no involvement	0.75	0.60–0.93	0.01
≥25% versus no involvement	1.03	0.83–1.29	0.77
Objective response rate			
Gender (M versus F)	1.30	0.86–1.96	0.21
Schedule (chrono versus conv)	1.23	0.79–1.91	0.36
Gender × schedule	0.46	0.26–0.81	0.008
Performance status (1 and 2 versus 0)	1.47	1.10–1.98	0.01
No. of sites			
2 versus 1	1.35	0.98–1.85	0.065
>2 versus 1	1.87	1.19–2.95	0.007
Percent liver involvement			
<25% versus none	0.58	0.38–0.89	0.012
≥25% versus none	0.97	0.63–1.51	0.91
Trial			
#2 versus #1	1.27	0.75–2.16	0.37
#3 versus #1	1.03	0.65–1.65	0.88

Table 2. Multivariate analysis of overall survival, progression-free survival and objective response rate

Homogeneity tests confirmed the consistent significant interaction between gender and treatment for OS, PFS and response rate among the three trials and the meta-analysis (Figure 1A). The significant interaction

terms found for each end point revealed a differential effect of schedule on outcomes in males and females, which was then modeled separately (supplementary material S2 and S3, available at Annals of Oncology online).

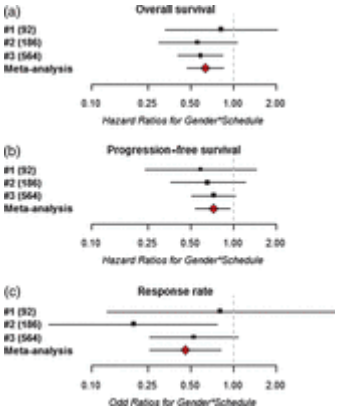

Figure 1 Interaction between sex and treatment effects. Results of equality of the hazard ratios for overall survival and progression-free survival (PFS) and those of the odds ratios for the response rate. Hazard ratios in each trial and in meta-analysis for (a) overall survival (P from Cochran's Q-test = 0.45), (b) PFS (P = 0.90); (c) odds ratio for the response rate (P = 0.50).

Effect of infusional schedule on antitumor efficacy according to gender

In males, OS was significantly prolonged on chronoFLO when compared with CONV (P from log-rank = 0.009) (Figure 2a). Corresponding median values were 20.8 months (18.7 to 22.9) and 17.5 months (16.1 to 18.8). Conversely, females on chronoFLO displayed a poorer OS when compared with CONV (P from log-rank = 0.012) (Figure 2b), with respective median values of 16.6 months (13.9 to 19.3) and 18.4 months (16.6 to 20.2). The 5- and 9-year survival rates of males were 14.4% (9.9 to 18.9) and 9.2% (5.3 to 13.1) on chronoFLO when compared with 7.9% (4.6 to 11.2) and 3.8% (0.7 to 6.9) on CONV. At 5 and 9 years, 5.3% (2 to 8.6) and 4.4% (1.3 to 7.5) of females survived on chronoFLO when compared with 15.6% (9.9 to 21.3) and 9.6% (3.9 to 15.3) on CONV.

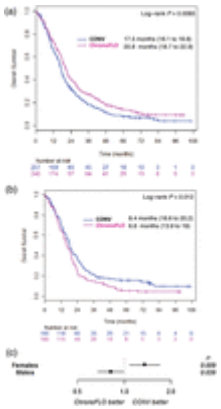

Figure 2 Sex differences in response to drug delivery schedule for overall survival. The Kaplan–Meier survival curves in males (a) and female (b), and Forest plot of interaction between schedule and gender (c).

Similar trends were found for both secondary efficacy end points (supplementary material S4, available at Annals of Oncology online). A trend toward a better PFS was found in males on chronoFLO rather than CONV (P = 0.088), with respective median values of 9.3 months (8.4 to 10.3) and 8.4 months (7.5 to 9.3). PFS was shorter in females on chronoFLO when compared with CONV (P = 0.031), with respective median

values of 7.4 months (6.2 to 8.5) and 8.2 months (6.8 to 9.6). The response rate was significantly higher in males on chronoFLO when compared with CONV (51.6% versus 37.8%, respectively, $\chi 2$ P = 0.002). In contrast the response rate in females was 38.3% on chronoFLO and 43% on CONV ($\chi 2$ P = 0.38). These relationships were adjusted for the potential prognostic factors already considered in the whole population model.

Forrest plots and sex-specific multivariate analyses confirmed that there was a lower risk of an earlier death on chronoFLO for males with an HR of 0.82 (0.68 to 0.99) (P = 0.039) and a higher risk for females with an HR of 1.36 (1.08 to 1.70) (P = 0.009) (Figure 2c and supplementary material S2, S3, S5, available at Annals of Oncology online). Similar trends were found for PFS in males. Thus, the HR of an earlier progression on chronoFLO when compared with CONV was 0.86 (0.72 to 1.03) in males (P = 0.11) and 1.27 (1.02 to 1.58) in females (P = 0.035). For the response rate, the odds ratio of an ORR on chronoFLO was significantly higher in males, being 0.55 (0.36 to 0.80) (P = 0.002), while no significant schedule effect was found in females.

DISCUSSION

This meta-analysis of three international randomized trials demonstrated that sex of a patient was the single significant predictor of the relative advantage of chronomodulated chemotherapy as the most effective delivery schedule of 5-FU-LV-oxaliplatin. The combination of these three drugs ranks among the most widely used regimens for treating patients with metastatic colorectal cancer. Here, the efficacy was assessed in 842 patients using the three most commonly used end points, i.e. OS, PFS and tumor response rate. Using stringent methods, sex was shown to be the single robust predictor of the treatment schedule achieving best ORR, best PFS and best OS, at univariate and multivariate or logistic analyses. For these three end points, males did better on chronoFLO than on CONV and females did better on CONV than on chronoFLO, independently of all known baseline patient characteristics.

In 2012, first-line chemotherapy of this disease still involves 5-FU-LV, oxaliplatin and/or irinotecan [12–14]. No other effective drug was available for the patients failing protocol treatment in Trials 1 or 2. Irinotecan was the only second-line active drug given to the patients in Trial 3. No targeted agent was available. Despite such limited second line options, the median OS times in our study were consistent with those reported in recent phase III trials [12, 15]. Neither bevazucimab, cetuximab nor panitumumab improved survival when added to first-line FOLFOX either in unselected populations or in patients whose tumor displayed no KRAS mutation [12–14]. In contrast, we show here that chronoFLO significantly enhanced median OS by 3.3 months when compared with conventional delivery of the same three drugs in males. This finding supports the chronomodulated administration of 5-FU-LV-oxaliplatin as an important step for improving the outcome for male patients with metastatic colorectal cancer. The chronomodulation of 5-FU-LV and oxaliplatin in combination with cetuximab was both safe and effective in first-, second- or third-line treatment [16]. Cetuximab could further enhance the efficacy of chronotherapy against colorectal cancer through amending the circadian disruption associated with elevated circulating levels of TGFα, an EGFR ligand [17].

The majority of patients alive at 9 years may be considered cured from a disease usually deemed as incurable [18]. Here, this was achieved in 9.2% of the male patients treated with chronoFLO and 9.6% of the females receiving a conventional infusion of the same three drugs.

Conventional therapy for localized colorectal cancer produced a better survival outcome in females when compared with males, in randomized trials involving over 1000 patients [19]. This finding is in good agreement with the better survival of females when compared with males on conventional chemotherapy

in the current meta-analysis. However, sex is seldom identified as an independent prognostic factor in clinical trials involving patients with colorectal cancer, since it is not usually examined as a possible source of interaction between the treatments under comparison. In a recent trial, panitumumab added to FOLFOX significantly prolonged PFS in males but not in females with metastatic colorectal cancer carrying no KRAS mutation [13]. This finding highlights the need to examine treatment effects separately in males and in females, as recently advocated [20].

Different phenotypic and genotypic profiles were reported in male and female primary colorectal cancers. Females had more right-sided tumors and a greater incidence of microsatellite instability (MSI), which was shown to predict for prolonged survival [21]. Males with mainly left-sided tumors did not benefit from adjuvant chemotherapy, while females with predominantly right-sided tumors did [21]. BRAF mutations were more frequent in stage II or III colon cancer in females when compared with males. BRAF mutation was an independent prognostic factor for survival outcome [22]. The presence of a functional EGFR polymorphism in colorectal cancer further predicted for a better survival in women and a worse one in men, when compared with patients of either sex with wild-type EGFR tumor [23].

Experimental data show that the endocrine system regulates circadian drug metabolism as well as the circadian timing system itself. Androgens regulate the circuitry in the hypothalamic circadian pacemaker, with functional consequences for clock gene expression and behavioral responses to photic stimuli in mice [24]. However, our study did not reveal any significant trend as a function of age in females or in males, which suggests that sex hormone played little role in the sex effect shown here.

Excessive hematologic and non-hematologic toxicities have been reported in females on 5-FU-based conventional chemotherapy [25, 26]. This sex-dependent toxicity could result from differences in drug metabolism and detoxification. Thus, 5-FU clearance as well as dihydropyrimidine dehydrogenase (DPYD) activity, its main determinant, were down-regulated in females when compared with males [27].

Strikingly, however, the prediction of 5-FU toxicity with DPYD gene polymorphism was robust and highly statistically significant in males but not in females, a finding which supports gender-specific toxicity mechanisms [25]. The severe toxicity associated with 5-FU-based regimens affects females 20% to 50% more frequently than males. The occurrence of neutropenia during treatment was identified as an independent prognostic factor of longer survival in chemo-naïve patients on FOLFOX for metastatic colorectal cancer [28]. This was confirmed in patients treated with FOLFOX2 in Trial 3 of this meta-analysis [29]. In this same trial however, males on chronoFLO displayed both less neutropenia and better survival when compared with females [9]. These findings further highlight distinct schedule-dependent relations between toxicity and efficacy [1, 29, 30]. Therefore, the current meta-analysis extends the clinical relevance of sexual dimorphism beyond 5-FU metabolism and the first shows the critical role of sex for the optimal circadian scheduling of chemotherapy in cancer patients.

Chemotherapy can indeed disrupt the circadian timing system, thus impair the coordination of drug metabolism and pharmacodynamics over the 24 h cycle [1]. Indeed, 12 anticancer drugs dampened, phase-shifted and/or suppressed physiological and molecular circadian rhythms as a function of dose and dosing time in experimental models [1]. Transforming growth factor-α, interleukin-6 and tumor necrosis factor-α not only accelerate cellular proliferation but also impair circadian physiology and/or molecular clocks [1]. High circulating levels of these three cytokines were associated with circadian disruption and poor survival in patients with metastatic colorectal cancer [17].

We hypothesize that the effect seen in our study stems from a sex-specific response of the circadian timing system to cancer and/or its treatment. Both experimental and human data support a better stability of circadian rhythms in males when compared with females [1, 30, 31]. Yet, the optimal chronomodulated schedule could also differ between male and female patients [32]. There were over 2000 rhythmic transcripts in males and females but only several hundred were common to males and females and peaked at a similar time of day. Both the circadian amplitude of melatonin secretion and that of core body temperature, as well as the entrainment properties of the circadian timing system also differed between male and female human subjects [31, 32].

In summary, this meta-analysis, using individual patient data from three chronotherapy trials, revealed sex as a robust determinant of the chemotherapy delivery schedule which offered best survival in patients with metastatic colorectal cancer. Ongoing research explores optimal chemotherapy timing in females based on the monitoring of circadian biomarkers. Meanwhile the current chronoFLO schedule validated here deserves prospective assessment as a safe and more effective first-line treatment option than conventional delivery for male patients with metastatic colorectal cancer.

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ARTBC Internationale, P. Brousse Hospital, Villejuif, France.

DISCLOSURE

The authors have declared no conflicts of interest.

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