Prediction of overall survival through circadian rest-activity monitoring during chemotherapy for metastatic colorectal cancer.

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Abstract

The clinical relevance of circadian rhythm modifications in patients on chemotherapy is unknown. Even so, circadian parameter I<O before chemotherapy independently predicted overall survival. This study investigates the relevance of I<O measured during chemotherapy for survival and symptoms. The circadian rest-activity pattern was monitored for 3 days using a wristwatch actigraph while 77 patients were receiving a chemotherapy course within an international randomized Phase III trial. Treatment consisted of first-line chronomodulated or conventional delivery of 5-fluorouracil, leucovorin and oxaliplatin for metastatic colorectal cancer. I<O was computed as the percentage of minutes of activity counts in bed which were below the median of activity out of bed. Circadian disruption was defined by I<O equal to or less than 97.5%. Circadian disruption occurred in 39 patients (51%) on chemotherapy. It was associated with a significantly shorter overall survival, independently of other prognostic factors (multivariate Hazard Ratio: 2.12; p = 0.004). The median survival of patients with a robust circadian rhythm was 22.3 months as compared to 14.7 months in those with circadian disruption during chemotherapy. No toxicity was significantly associated with circadian disruption, but the incidence of grade ≥2 fatigue and of body weight loss ≥5% was two and threefold higher, respectively, in patients with disrupted circadian rhythm on chemotherapy. Chemotherapy disrupted circadian activity rhythm in nearly 50% of the patients. Circadian disruption on chemotherapy predicted for shorter overall survival. The prevention of chemotherapy-induced circadian disruption might reduce toxicity and improve efficacy in cancer patients.

Introduction

Modern chemotherapy protocols have lead to an improvement in the survival of patients with metastatic colorectal cancer.1 However, these regimens also produce substantial systemic and organ-related toxicities, with a negative impact on patients' wellbeing.2 In particular, chemotherapy-induced fatigue and anorexia are frequent and bothersome complaints of cancer patients undergoing anticancer treatment, for which available pharmacological treatment is usually not very effective.3–5 These symptoms cluster frequently in cancer patients, with a possible immuno-neuroendocrine mechanism underlying their pathogenesis.6–9 The scientific evidence supporting this mechanism suggests that a disruption of the circadian timing system could be implicated.3, 10, 11

The circadian timing system is hierarchically organized so as to rhythmically control several psychological and physiological functions, at physiological, cellular and molecular levels, over the 24 hr.12 This is the basis for studies of the administration of anticancer agents at defined times along the 24 hr, so-called chronotherapy.13, 14 The tight circadian coordination of biological functions from cells to whole organism plays an important role in cancer progression.14 A severe disruption of the circadian timing system through ablation of the hypothalamic pacemaker, or iterative alterations of the day–night cycle or clock gene mutations were found to accelerate experimental cancer progression.15–17 Conversely, enhancement of circadian coordination through regular meal timing slowed down experimental cancer growth.13, 14, 16, 18

The circadian timing system of cancer patients can be evaluated through noninvasive monitoring of the rest-activity pattern using a wristwatch actimetry device.19, 20 The rest-activity rhythm is a validated biomarker of the circadian pacemaker in the hypothalamus both in experimental models and in humans.21 Although the proper use of circadian should be reserved for studies performed in constant conditions, we use here the term circadian for daily rhythms also measured under environmental entraining cues. The rest-activity records gathered by the wristwatch actimetry device allow the computation of the relative amount of activity in-bed versus out-of-bed (I<O). This parameter was identified as a quantitative and clinically relevant circadian estimate in three cohorts involving a total of 436 patients with metastatic

colorectal cancer, whose rest-activity pattern was monitored before receiving a new chemotherapy protocol.22–24 Median survival was nearly twice as high in patients with metastatic colorectal cancer whose baseline I<O exceeded 97.5% as compared to those with a lower I<O before chemotherapy delivery.22, 24 Several studies have also reported a significant association between fatigue, anorexia or weight loss and altered circadian function in cancer patients.3, 22, 24–28

Chemotherapy has been found to disrupt circadian rhythms in rest-activity, core body temperature, corticosterone secretion and clock gene mRNA transcription as a function of dose and circadian timing in mice or rats.14, 29, 30 However, neither the occurrence of circadian disruption during chemotherapy nor its correlation with toxicity and survival have been systematically assessed in cancer patients. Here, we used data from a prospective companion study to an international randomized Phase III trial (EORTC05963) to carry out exploratory transversal and longitudinal analyses. The trial involved patients receiving first-line chemotherapy for metastatic colorectal cancer. The aim of this study was to investigate the impact of chemotherapy-induced circadian disruption on survival, and to identify the toxic symptoms associated with such disruption, in patients undergoing chemotherapy for metastatic colorectal cancer.

Patients and Methods

Study population

This is a secondary analysis of prospectively collected data within an international, randomized, controlled open Phase III trial, EORTC 05963.31 In this trial, 564 patients with previously untreated metastatic colorectal cancer were enrolled at 36 Institutions, from October 1998 to February 2002. After signing an informed consent, patients were randomized to receive either a 4-day chronomodulated (chronoFLO4) or a 2-day conventional (FOLFOX2) delivery schedule of oxaliplatin, folinic acid and 5-fluorouracil. The trial was approved by the ethics committee in each centre and/or country and was conducted in accordance with the Helsinki declaration.31 A subset of patients on this study at nine Institutions (four countries) participated in a prospective companion translational study involving rest-activity monitoring.24 Data from these patients were used for the current study. Here we report, for the first time, the correlation between the circadian rest-activity pattern evaluated during and immediately after chemotherapy delivery with efficacy outcomes and toxicity.

Patients had their rest-activity pattern monitored with a wrist actimetry device within 7 days from the start of a chemotherapy course, with corresponding toxicity data for the same treatment course documented. When multiple rest-activity time series were available for the same patient, only the first one was used. A recent publication, further reported a transient alteration in circadian rest/activity rhythm during the first week of chemotherapy, with subsequent recovery.32, 33 On the basis of these reports, we limited our analysis to the data obtained during the first week following chemotherapy administration.

Circadian rest/activity rhythm assessment

Individual locomotor activity was monitored noninvasively using a Mini-Motionlogger actimetry device (Ambulatory Monitoring Inc., USA) for at least 72 hr. This watch-sized piezoelectric linear accelerometer has a memory chip for data storage and continuously records the number of nondominant-wrist accelerations per minute.19, 20, 22, 24 Actimetry time series were analyzed using a dedicated program (Action 4, version 1.10; Ambulatory Monitoring Inc., USA) to provide a robust, well-characterized and clinically meaningful parameter, the dichotomy index (I<O), to estimate individual circadian rest/activity pattern.22, 24, 25 This dichotomy index provides an integration of the circadian regulation of sleep and

activity and represents the percentage of minutes during the rest span when activity is lower than the median activity during wakefulness.34 In the case of a robust and marked circadian rest-activity pattern, I<O approaches or reaches 100%. The lower the I<O value the more severe the disruption of the circadian rest-activity rhythm. Here, we defined circadian disruption during chemotherapy as a value for I<O lower than or equal to 97.5%, based on results from a pooled analysis of rest-activity records obtained from 436 patients with metastatic colorectal cancer in the absence of chemotherapy administration.23

Clinical outcomes

Overall incidence of severe or life-threatening toxicity was calculated throughout the treatment span, according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The best objective tumor response on treatment was evaluated and rated according to the WHO criteria. Overall and progression-free survival durations were computed from the first day of rest-activity monitoring until the event date or the last contact date. The database was updated and locked on November 2007.

Toxicity assessment

Clinical and hematological toxicities were assessed at least fortnightly and graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Patient's weight was measured before each course was administered. The toxicity data used here were limited to the worst grade of each type of toxicity experienced by the patient during the interval between the beginning of the course preceding and that following rest-activity monitoring.

Hematological (anemia, thrombocytopenia, leucopenia and neutropenia) and clinical toxicities (diarrhea, mucositis, hand-foot syndrome, peripheral sensory neuropathy, nausea and vomiting, fatigue and body weight loss) were assessed. No data were available for anorexia. Based upon previous reports showing a significant association between fatigue or weight loss and altered locomotor activity rhythm before or off chemotherapy,3, 22, 24–26 we considered these two events separately from the other toxicities, for which no association with circadian dysfunction has been reported to date. Clinical relevance was attributed to Grade 2 or 3 fatigue35 or grade 1 body weight loss, corresponding to 5% or more within 2 weeks.36 The other toxicities were considered as clinically relevant if they were of Grade 3 or more.

Statistical analyses

The main endpoint of this study was to document the clinical impact of circadian disruption during chemotherapy on overall survival. First, overall survival curves were compared according to circadian disruption (I<O less than or equal to 97.5%) or robustness (I<O greater than 97.5%), using the Kaplan–Meier method and the logrank test. Then, Cox multivariate hazard modeling was performed adding sex, treatment schedule, number of metastatic sites, rank of chemotherapy course with actimetry and Performance Status on day 1 of the course as fixed covariates in order to explore the independent prognostic value of circadian disruption during chemotherapy. Secondary aims included the evaluation of the impact of circadian disruption on chemotherapy on other clinical outcomes, the documentation of its incidence and the identification of its associated clinical features and toxic events. The clinical and demographic characteristics considered included age, sex, site of primary tumor, number of metastatic sites, performance status (PS) both at trial entry and before actimetry (WHO scale), categorized body mass index at study entry, randomized treatment schedule, number of chemotherapy courses given before actimetry, the interval in days between actimetry recording and chemotherapy cycle start, as well as the corresponding doses of oxaliplatin and 5-fluorouracil.

Exploratory analyses involved two-sided Fisher's exact test for categorical variables and a Mann-Whitney U test for quantitative parameters. The tests enabled comparisons of clinical features or toxic events according to I<O values above versus equal to or lower than 97.5%. Multivariate binary logistic regression was used in order to identify the clinical features and toxicity events associated with circadian disruption during chemotherapy. The assumption of a normal distribution of I<O was tested using the Kolmogorov-Smirnov test. Missing data for any parameter were not imputed and percentages reported here refer to available data for each variable. The threshold for statistical significance was set at 5%. Analyses were performed using PASW Statistics 18 software (SPSS Inc., USA).

Results

Clinical and demographical characteristics

Seventy-seven patients fulfilled the inclusion criteria, with locomotor activity being recorded during or within the week following the first day of administration of a chemotherapy course. This represented 13.7% of the whole population of the patients registered in the Phase III trial and 40.3% of those enrolled at the Institutions participating in the companion translational study. The main clinical and demographical characteristics and the overall outcomes of the current study patients were similar to those of the whole trial population31 (Table 1).

Table 1. Clinical and demographical characteristics of the 77 patients in the current study, according to the presence or absence of circadian disruption during chemotherapy

Feature		Circadian disruption		Total study popula
		No ($n = 38$)	Yes ($n = 39$)	($n = 77$)
Treatment arm (%)	FOLFOX2	52.6	48.7	50.6
	chronoFLO4	47.4	51.3	49.4
Gender (%)	Females	31.6	38.5	35.1
	Males	68.4	61.5	64.9
Age (years)	Median (Range)	60.5 (33.2–75.5)	64.3 (27.4–75.0)	62.3 (27.4–75.5
	1st–3rd quartiles	54.1–66.3	52.2–69.3	52.9–68.4
Site of primary tumor (%)	Colon	76.3	78.9	77.6
	Rectum	23.7	21.1	22.4
Number of metastatic sites (%)	1	31.6	42.1	36.8
	2	52.6	34.2	43.4
	≥ 3	15.8	23.7	19.7
PS (WHO) at study entry (%)	0	76.3	66.7	72.4
	1	18.4	28.2	22.4
	2	5.3	5.1	5.3
BMI (Kg/m^2) at study entry (%)	Normal (18.5–24.9)	42.1	50.0	46.1
	Abnormal	57.9	50.0	53.9
Ranking of chemotherapy cycle of actimetry	Median (range)	4 (1–9)	4 (1–9)	4 (1–9)
	1st–3rd quartiles	2–5	2–5	2–5
Interval between actimetry and chemotherapy cycle start (days)	Median (range)	2 (1–6)	1 (0–7)	1 (−1–7)
	1st–3rd quartiles	0–4	0–5	0–4
PS at the cycle of actimetry (%)	0	63.2	56.4	59.7
	1	36.8	35.9	36.4
	2	0	7.7	3.9
PS change following actimetry (%)	Worsening	7.9	8.6	6.8
	No change	86.8	82.9	84.9
	Improvement	5.3	8.6	8.2
Administered dose of Oxaliplatin (mg/sqm) at the cycle of actimetry	Median (range)	100 (0–107)	100 (80–107)	100 (0–107)
	1st–3rd quartiles	99–100	100–100	99–100
Administered dose of 5-Fluorouracil (g/sqm) at the cycle of actimetry	Median (range)	3.40 (2.20–3.71)	3.40 (1.83–3.66)	3.40 (1.83–3.71
	1st–3rd quartiles	3.00–3.60	3.06–3.60	3.00–3.60
Course duration (days)	Median (range)	14 (12–49)	14 (13–29)	14 (12–49)
	1st–3rd quartiles	14–19	14–21	14–21
Oxaliplatin dose reduction following the cycle of actimetry (%)	Yes	13.2	13.5	13.3
5-Fluorouracil dose modification following the cycle of actimetry (%)	Reduction	15.8	10.8	13.3
	Escalation	21.1	21.6	21.3
Objective Response Rate (%)	Yes	52.6	47.4	50.0
Progression Free Survival (months)	Median (95% CL)	8.2 (6.2–10.3)	7.3 (4.2–10.3)	7.9 (6.9–8.8)
Overall Survival (months)	Median (95% CL)	22.3 (19.6–25.1)	14.7 (11.8–17.6)	20.2 (14.4–26.0
Overall G$\geq$3 Toxicity (%)	Yes	73.7	71.1	72.4

Timing of actimetry monitoring

A median of five chemotherapy courses (range, 1 to 9) was given before the current “on treatment” wrist-actimetry monitoring (Fig. 1a). Recording took place during chemotherapy delivery itself for 80.5% of the patients. The median interval between the onset of chemotherapy and that of actimetry was one day (Fig. 1b).

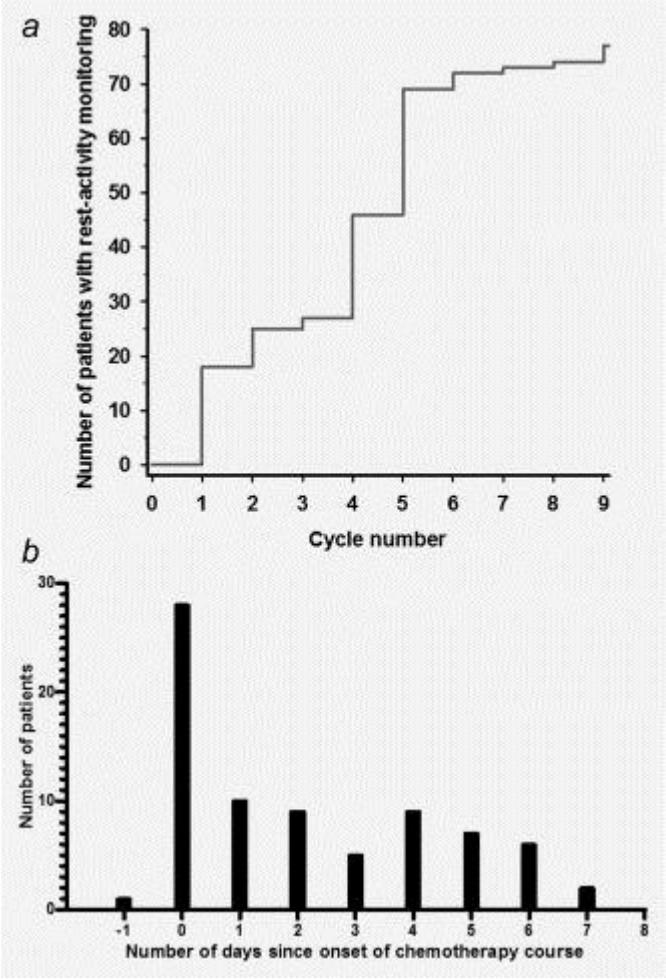

Figure 1.

Timing of actimetry in relation to chemotherapy. Panel a: cycle rank following which locomotor activity was recorded. Panel b: interval in days between the beginning of the administration of the chemotherapy course and the beginning of wrist actimetry.

I<O distribution

The distribution of I<O was not normal ($p < 0.0001$). The respective median and mean values of I<O were 97.5% (interquartile range, 5.3%) and 95.1% (standard deviation, 7.8%) (Fig. 2). The median I<O value corresponded exactly to the cut-off value previously selected for defining circadian disruption. Thus, the 39 patients with altered circadian rest-activity rhythm (i.e., I<O lower than or equal to 97.5%) represented 50.6% of the current study population (Table 1; Fig. 2). Patients with circadian disruption displayed a median I<O of 93.8% (range: 42.3% to 97.5%), whilst the median I<O value of the patients with a robust circadian rest-activity rhythm was 98.9% (range: 97.6% to 100%). Overall, the distribution pattern of I<O on

treatment strongly resembled that reported at baseline in two independent cohorts involving 130 and 170 patients with metastatic colorectal cancer patients, respectively.22, 24, 25

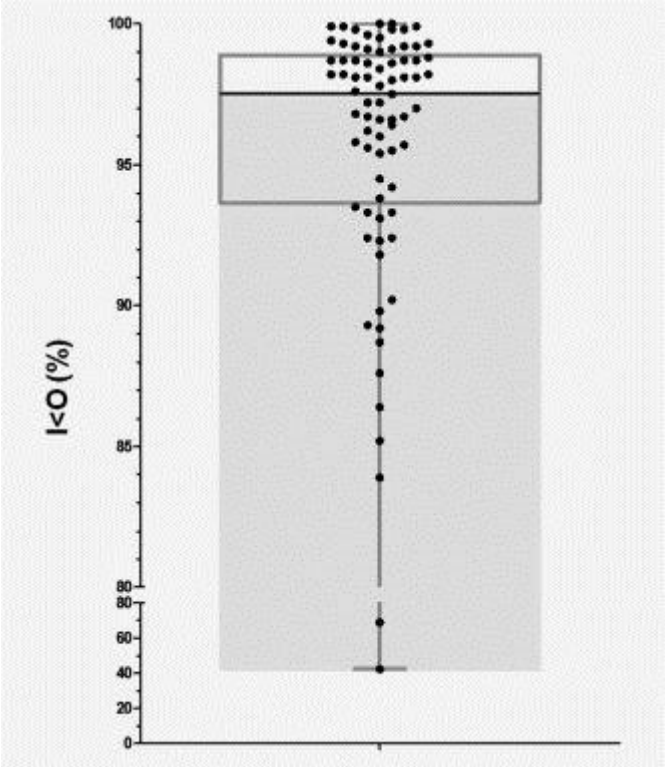

Figure 2.

Distribution of the parameter I<O in the current study population. I<O values ≤ 97.5% define circadian disruption and are in the gray area. Each dot represents a patient and the bars represent the median (97.5%) with the 1st and 3rd quartiles and the whiskers show the range.

Circadian disruption during chemotherapy and clinical outcomes

No statistically significant difference was found for objective response rate (p = 0.82), progression-free survival (p = 0.79) and overall Grade 3–4 toxicity rate (p = 0.80) according to I<O value (Table 1). Conversely, overall survival was significantly longer in the patients with a robust circadian rhythm as compared to those with circadian disruption (p = 0.013) (Fig. 3; Table 1). The negative prognostic value of circadian disruption during chemotherapy remained statistically significant after adjustment for sex, treatment schedule, number of metastatic sites, rank of chemotherapy course of interest and PS on day1 according to a Cox model (Table 2) (p = 0.004). Thus, the patients with an altered rest-activity circadian rhythm during chemotherapy displayed an independent and doubled risk of an earlier death following rest-activity monitoring as compared to the patients with a robust circadian rhythm (Hazard Ratio: 2.12; 95% CL: 1.27–3.54) (Table 2).

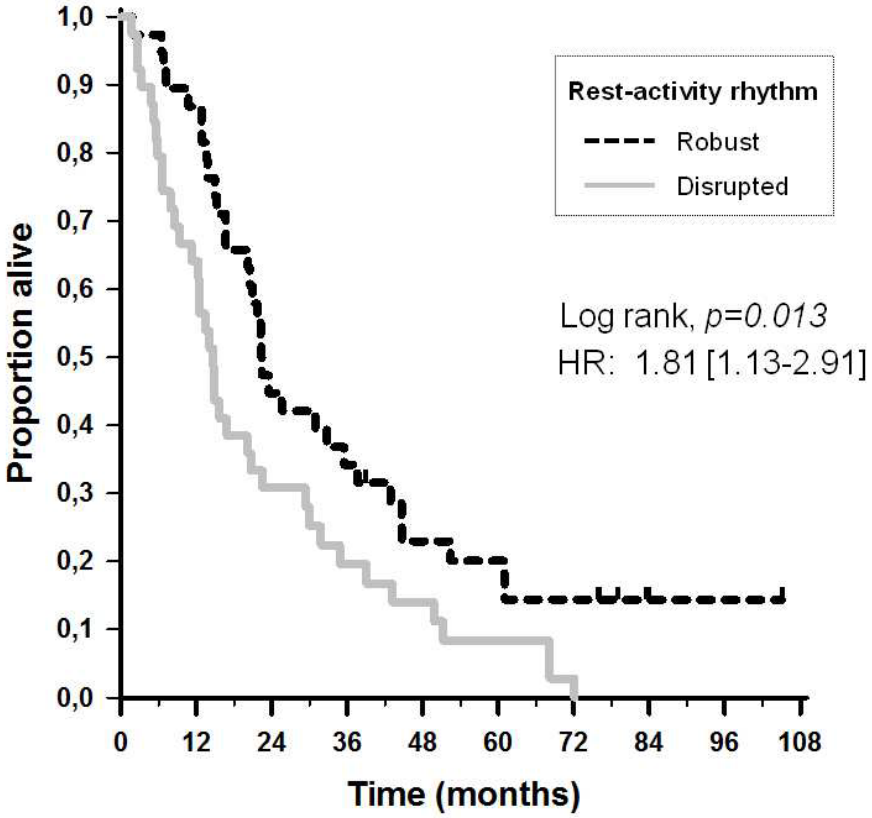

Figure 3.

Kaplan–Meier curves depicting overall survival, computed from the beginning of actimetry according to the persistence of marked circadian function (black dashed line) or the occurrence of circadian disruption (solid gray line). p-Value derived from a logrank test. Hazard ratio derived from a univariate Cox proportional hazard model.

Table 2. Multivariate proportional hazard model for overall survival

Parameter		Univariate		Multivariate	
		HR (95% CL)	p	HR (95% CL)	p
Circadian disruption	No (I<O > 97.5%)	1	**0.014**	1	**0.**
	Yes (I<O ≤ 97.5%)	**1.81 (1.13–2.91)**		**2.12 (1.27–3.54)**	
Treatment schedule	FOLFOX2	1	0.61	1	0.
	chronoFLO4	0.89 (0.55–1.42)		0.72 (0.44–1.20)	
Gender	Female	1	0.78	1	0.
	Male	0.93 (0.57–1.53)		1.07 (0.64–1.79)	
Number of metastatic sites	1	1	0.20	1	0.
	2	1.64 (0.95–2.82)		2.05 (1.14–3.68)	
	≥ 3	1.34 (0.67–2.69)		1.62 (0.75–3.53)	
Rank of chemotherapy course	(Quantitative)	0.98 (0.88–1.09)	0.71	1.01 (0.88–1.15)	0.
PS[1]	0	1	0.25	1	0.
	1	1.25 (0.75–2.09)		1.45 (0.82–2.60)	
	≥ 2	2.03 (0.85–4.87)		1.64 (0.62–4.34)	

[1]PS (WHO criteria) at day 1 of the chemotherapy course of actimetry. Significant results in bold.
Abbreviations: HR: hazard ratio; 95% CL: confidence limits at 95%.

Circadian disruption and clinical features

The baseline clinical characteristics of the patients at study entry were similar regardless of the subsequent occurrence of circadian disruption on chemotherapy (Table 1). No difference in any feature related to the chemotherapy course of interest was observed between patients with circadian disruption and those with a robust circadian rhythm (Table 1). The duration of the course of chemotherapy of interest and the related rates of cycle delay or dose modifications were similar in the subgroup of patients with circadian disruption and that of patients with a robust circadian rhythm (Table 1). Exploratory statistical comparisons between patients with altered or robust circadian rest-activity rhythm on chemotherapy showed no statistically significant difference according to age ($p = 0.48$), PS ($p = 0.60$), BMI ($p = 0.65$), number of metastatic sites ($p = 0.48$), site of primary tumor ($p = 0.49$), actual administered dose of oxaliplatin ($p = 0.99$) or 5-fluorouracil ($p = 0.93$), PS on first day of the treatment course of interest ($p = 0.22$), course rank ($p = 0.46$), duration of chemotherapy course ($p = 0.78$), or timing of actimetry in relation to course onset ($p = 0.45$). The incidence of circadian disruption during chemotherapy did not significantly differ according to gender ($p = 0.64$) or treatment schedule ($p = 0.71$). The highest incidence of circadian disruption was observed in females on chronoFLO4 (64.3%) as compared to the other three subgroups (≤50.0%).

Factors predicting the occurrence of circadian disruption during chemotherapy

Univariate and multivariate binary logistic regressions failed to identify any clinical or biological parameter significantly predicting the occurrence of altered circadian rest-activity rhythm on treatment ($p \geq 0.13$; details not shown).

Baseline actimetry was available before the start of chemotherapy for 44 of the 77 patients. Half of them ($n = 22$) had I<O lower than or equal to 97.5%. Baseline circadian disruption did not predict subsequent circadian disruption during chemotherapy ($p = 0.23$; details not shown). Moreover, no significant correlation was found between baseline and “on treatment” I<O values ($r = 0.15$; $p = 0.35$).

Toxicity

Overall, 12 patients (16.0%) experienced Grade ≥ 2 fatigue, and four patients (5.6%) lost 5% or more of their body weight, after the chemotherapy course of interest. Both symptoms occurred simultaneously in two patients. Grade ≥ 3 clinical or hematological toxicities occurred in 10 patients (13.0%), with each kind of toxicity being infrequent (≤ 10.8%, not shown). Thirty-four patients (44.2%) displayed Grade 2–4 clinical or hematological toxicities besides fatigue or body weight loss. Performance status worsened in six patients (8.2%), and improved in 5 patients (6.8%), following the cycle of actimetry recording (Table 1). The overall rate of missing information on toxicity, performance status or body weight was 27/1155 variables (2.3%).

Circadian disruption and toxicity

The incidence of circadian disruption during chemotherapy was comparable among the patients whose PS deteriorated (50.0%), remained unchanged (46.8%) or improved (60.0%) following the administration of the chemotherapy course of interest (p = 0.85). The low incidence of clinically relevant fatigue and body weight loss precluded any statistical validation of differences according to I<O values (p = 0.35). However, chemotherapy-induced fatigue of Grade 2 or higher occurred twice as often in patients with circadian disruption (n = 8; 21.1%) as compared to those with a robust circadian rhythm (n = 4; 10.8%) (Fig. 4). Similarly, body weight loss ≥5% occurred three times as frequently in patients with altered rest-activity circadian rhythm (n = 3; 8.6%) as compared to those with a robust rhythm (n = 1; 2.7%) (Fig. 4). The incidence of other grade ≥3 clinical or hematological toxicities during the chemotherapy course of interest was similar in patients with low (n = 5; 12.8%) or high (n = 5; 13.2%) values for I<O (p = 0.96) (Fig. 4). Overall, absent or mild toxicities were more frequent in patients with a robust circadian rhythm despite chemotherapy as compared to patients with a disrupted circadian rest-activity rhythm (65.8% vs. 46.2%; p = 0.11).

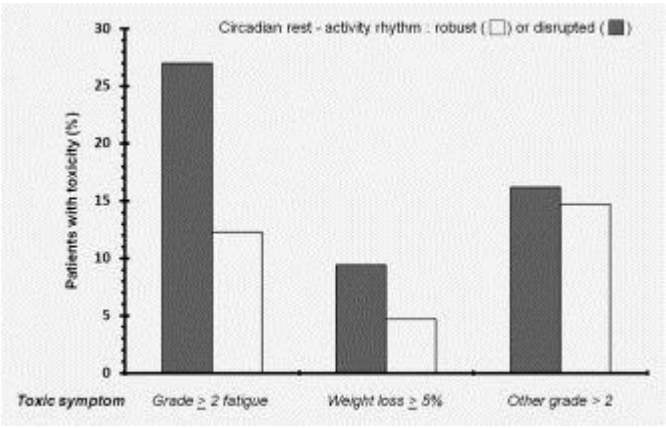

Figure 4.

Incidence of clinically relevant toxicities in the subgroups of patients with robust (white bars) or disrupted (gray bars) circadian rest/activity rhythm.

Discussion

In this international study, we explored the associations between circadian disruption during chemotherapy and treatment-induced adverse events and clinical outcomes. The status of the circadian timing system was estimated using noninvasive recording of locomotor activity with a wristwatch actimetry device, and the computation of a robust and validated circadian parameter, the dichotomy index (I<O).22, 24, 25, 34 Data from a pooled analysis of 436 patients with metastatic colorectal cancer allowed the identification of a cut-off value of 97.5% for I<O, below which the patients incurred clinically relevant circadian disruption.23

A transversal design was used to describe and compare the incidence of chemotherapy-induced toxicities between patients with robust or altered circadian timing system. By contrast, a repeated measures approach has been used by other researchers to explore the dynamics of circadian or sleep functions during treatment and their correlations with the temporal evolution of a subjectively rated symptom, mainly fatigue.26, 28, 32, 37, 38 These studies have consistently described an inverse correlation between the patterns of fatigue and those of physical activity or sleep efficiency over time.26, 28, 32, 37, 38

Most importantly, our study shows that overall survival is significantly longer in the patients who display a robust circadian rest-activity rhythm during chemotherapy, as compared to those with circadian disruption, independently from other prognostic factors or experimental conditions. This result complements previous studies already documenting the independent prognostic value of baseline I<O for the overall survival of patients with metastatic colorectal cancer.22, 24 Also, this finding supports the hypothesis that undue chemotherapy-induced circadian disruption could lead to a deterioration in host mechanisms involved in cancer control and could shorten overall survival.14 Conversely, an improvement in circadian function during chemotherapy could reflect improved host control of tumor growth, with an associated better prognosis, as shown experimentally.16 However, the observational nature of the study does not provide any definitive evidence on the causal relationship between chemotherapy-induced circadian disruption and shorter overall survival.

This study has also examined the incidence of clinically relevant toxicities occurring during the chemotherapy course when circadian rhythm evaluation was performed. Previous studies in experimental models and in cancer patients have shown that chemotherapy can disrupt host circadian rhythms.14, 27, 28, 32 This novel and hitherto overlooked toxicity impacting the circadian timing system could potentially hinder the anticancer activity and the safety of cancer chronotherapy, whose foundations assume consistent and predictable circadian rhythms in those physiological and molecular parameters which mediate pharmacological effects and cancer proliferation.13, 14, 39 Here, the female patients on chronoFLO4 displayed the highest rate of chemotherapy-induced circadian disruption (64%) and the worst clinical outcomes in the Phase-III trial. Conversely, circadian disruption occurred in 46% of the current male patient sample on chronoFLO4, the subgroup which achieved best survival outcome in the same trial.31 These findings support the hypothesis that sex-related differences in the human circadian timing system properties40–42 could result in survival and tolerance disparities on chronotherapy,31, 43 thus implying that the optimal chronotherapy schedule might differ between men and women.

The small sample size and the low incidence of adverse events in our study precluded any statistical validation of differences in adverse events according to I<O. However, fatigue and weight loss occurred selectively and several times more often in patients with circadian disruption as compared to those with a robust circadian rhythm (Fig. 4). These findings concur with those of other studies reporting an association between circadian disruption and fatigue, anorexia and weight loss in cancer patients and in healthy subjects intolerant to shift work or jet lag.3, 22, 24–26, 44, 45 These symptoms frequently cluster as a consequence of the burden of cancer and in association with toxic chemotherapy,3, 46–49 suggesting shared underlying patho-physiological mechanisms. The circadian timing system, which temporally coordinates the main physiological functions, including physical performance and appetite,3, 13, 14, 39 could, when disrupted, be one of the main determinants in the pathogenesis of this symptom cluster, thus representing a potential treatment target.3

In our study, baseline circadian pattern did not seem to predict for forthcoming circadian robustness or disruption during chemotherapy administration, although the cohort of patients with both baseline and on-

treatment actimetry assessments consisted of only 44 patients, thus preventing any definitive conclusion on this issue. Indeed, we observed both improvement and worsening of circadian function during chemotherapy, as compared to baseline assessment, in agreement with findings in an independent cohort, evaluated with a continuous monitoring approach.33

Another limitation of the current study is related to the heterogeneity in the timing of actimetry in relation to treatment, in terms of course rank and toxicity assessment. However, no difference in the incidence of circadian disruption was found with regard to treatment timing (cycle number or days elapsed since onset of cycle) (Table 1), supporting the merging of all available data with regard to timing of actimetry. Moreover, this transversal approach gives a unique global assessment along the treatment span of the clinical and toxic correlates of circadian disruption during chemotherapy. However, whilst actimetry was performed for 72 hr during the initial week of the chemotherapy course, the precise timing of occurrence of the assessed toxicities was unknown and spanned the whole duration of the treatment course and subsequent treatment-free interval. The possible time lag between the occurrence of the toxic event and that of chemotherapy-induced circadian disruption was not considered in the current study. This could lead to an underestimate of the delved associations found between circadian disruption and toxicity. The current results support the future development of prospective and large studies using a continuous and repeated measures approach, as currently conducted in a companion translational study to the European phase II trial OPTILIV07 (ClinicalTrials.gov Identifier: NCT00852228).

In this study, we did not explore the possible mechanisms of chemotherapy-induced circadian disruption. There is, however, evidence that the release of proinflammatory cytokines following chemotherapy administration could account for the occurrence of altered circadian patterns and of systemic symptoms.3, 6, 10, 11, 48 This hypothesis deserves to be tested in future dedicated studies, since it could provide supplemental clues for potential innovative targeted interventional strategies.

In conclusion, we report here that chemotherapy-induced circadian disruption, as defined according to a validated quantitative cut off value for the parameter I<O, is an independent poor prognostic factor for overall survival. A value while on chemotherapy of I<O equal to or below this 97.5% predicts a doubled risk of earlier death and a 7.6 months reduction in estimated median survival as compared to higher I<O values while on chemotherapy (Fig. 3; Table 1). We also show here a higher incidence of clinically relevant fatigue and weight loss in patients with altered circadian function during chemotherapy administration. Thus, the occurrence of circadian disruption, whether cancer-related or chemotherapy-induced, is consistently associated with reduced survival, providing additional evidence for a role of the circadian timing system in cancer progression.15–18, 22, 24 The study further provides quantitative estimates that will inform the tailored design of prospective studies, which are warranted. Shielding the circadian timing system from chemotherapy-induced alterations, through chronotherapy optimization and/or specific pharmacological targeting, could become a novel therapeutic objective for simultaneously improving survival and reducing systemic symptoms in cancer patients on chemotherapy.14, 24, 50

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