Marked 24-h Rest/Activity Rhythms Are Associated with Better Quality of Life, Better Response, and Longer Survival in Patients with Metastatic Colorectal Cancer and Good Performance Status

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ABSTRACT

The rest/activity circadian cycle has been used as a reference for chemotherapy administration at specific times to improve tolerability and efficacy. Because cancer processes may be associated with alterations of circadian rhythms, the rest/activity cycle was monitored noninvasively to assess its relationship with tumor response, survival, and quality of life in 200 patients with metastatic colorectal cancer. Patients wore an actigraph, a wristwatch that records the number of accelerations per minute, for 3 days before receiving chronomodulated chemotherapy. The circadian rhythms in activity were estimated by two robust parameters: the autocorrelation coefficient at 24 h (r24), and the dichotomy index (I<0) for comparing amounts of activity when in bed and out of bed. Accurate data for inclusion, quality of life, response, and survival were available for 192 patients. Survival at 2 years was 5-fold higher (P = 10^-4) in patients with marked activity rhythm (I<0 in upper quartile) than in those with rhythm alteration (I<0 in lower quartile). These results were supported by the multivariate Cox analysis. Multivariate regression analysis showed that circadian rhythms in activity (I<0; P = 3 × 10^-4) and in WBCs (P = 0.03) as well as performance status (P = 0.02) were jointly prognostic of response. Patients with marked rest/activity rhythms also had better quality of life and reported significantly less fatigue. The individual rest/activity cycle provides a novel independent prognostic factor for cancer patients’ survival and tumor response as well as a quantitative indicator for quality of life.

INTRODUCTION

Locomotor activity reliably reflects circadian clock function in several animal species (1). The stereotaxic destruction of the suprachiasmatic nuclei, considered as the hypothalamic circadian clock, suppresses the rest/activity rhythm, whereas their transplantation restores it (2). Mutations in the genes involved in circadian regulation also induce profound alterations of the rest/activity cycle in Drosophila, hamsters, or mice (3–5).

In humans, the rest/activity rhythm is considered, and used as, a marker of the endogenous circadian clock function in isolation studies (6–8), in phase-shift studies (9–11), and in psychiatry (12–14). The rest/activity rhythm is a better marker of the human circadian system than cortisol or leukocytes, which interfere with and may be affected by peripheral physiological changes (reviewed in Ref. 15). However, the clinical relevance of the rest/activity rhythm has not yet been addressed in cancer patients.

The administration of anticancer agents at specific stages of the rest/activity cycle improves their therapeutic index in laboratory rodents (16). Time-qualified chemotherapy (chronotherapy) was first successfully used for ovarian cancer (17, 18). An appropriate adjustment of chemotherapy delivery to circadian rhythms became feasible with the advent of multichannel programmable pumps and led to the clinical validation of the chronotherapy principle in Phase I, II, and III clinical trials involving >1500 patients with metastatic colorectal cancer (19–22). More specifically, chronotherapy with 5-fluorouracil, leucovorin, and oxaliplatin reduced by 5-fold the incidence of severe mucositis, halved the incidence of functional impairment from peripheral sensory neuropathy, and nearly doubled the objective response rate compared with constant infusion (21). Nevertheless, interpatient variability was observed, indicating that factors other than the timing of treatment influenced outcome.

Cancer processes can alter circadian function in both experimental tumor models and patients (23). Thus, variability in the outcome of patients receiving chronotherapy may reflect differences in individual circadian rhythms. If so, these rhythms may constitute novel prognostic factors, possibly independent from the clinical factors, which mostly reflect tumor spread.
The status of the circadian system as an estimate of cancer patients’ prognosis was first tested in two pilot studies. The first study investigated individual rhythms in relation to clinical predictors for survival in 20 patients with advanced ovarian cancer. Significant correlations were found between well-documented prognostic factors, such as the WHO PS3 or tumor size, and the circadian amplitude in serum cortisol and leukocyte or neutrophil counts (27). The second study indicated that circadian rhythm alterations were associated with both poor PS and liver metastases in 13 patients with advanced breast cancer (28).

This prospective study was initiated to evaluate the prognostic value of circadian rhythms in patients with metastatic colorectal cancer. The primary hypothesis was that altered rest/activity rhythms would predict for shorter survival. Maximum tumor response and QoL were secondary end points of patient outcome. Additional exploratory analyses were performed to determine whether clinical prognostic factors, other marker circadian rhythms, or QoL factors such as fatigue, sleep disturbances, and pain significantly influenced the relationship between the rest/activity rhythm and survival.

**PATIENTS AND METHODS**

**Patients Selection and Clinical Study**

From May 1994 to January 1997, 200 consecutive ambulatory patients with histologically proven metastatic colorectal cancer, referred for chronomodulated chemotherapy, were registered in the study; 52% of the patients had two or more metastatic sites, and 59% had previously failed one to six chemotherapy lines before registration (Table 1). All patients were followed for survival until February 1, 1998, when 126 deaths were recorded. Patients in poor general condition, i.e., with PS, according to WHO, above 2, were not included in the study, as is usual in oncology clinical trials. The initial evaluation included a clinical examination, with PS assessment, thoracic and abdominopelvic computed tomography scan and liver echography. Serum CEA and CA19.9 were determined. Chronomodulated chemotherapy consisted of the association of 5-fluorouracil (3200–3500 mg/m²/course; peak delivery at 4:00 a.m.) and leucovorin (1200–1500 mg/m²/course; peak at 4:00 h); oxaliplatin was added to this two-drug regimen in 87% of the patients (100–125 mg/m²/course; daily maximum at 4 p.m.). Chronotherapy was delivered in fully ambulatory conditions to all patients, using a multichannel time-programmable pump (9–12). Circadian rhythms in serum cortisol and in leukocyte and neutrophil counts as well as the rest/activity cycle were studied before the first cycle of chronotherapy. Maximum tumor response to therapy was assessed every 2 months for the first 6 months by the investigators. Computed tomography scans of the thorax, abdomen, and pelvis were generally complemented with abdominopelvic ultrasonography and underwent extramural review. Complete response was defined as a disappearance of all signs of disease for 4 weeks, and partial response was defined as a reduction of at least 50% in the area of all measurable lesions (20, 21). The Ethical Committee of Kremlin-Bicêtre (France) approved the study, and each patient signed a written informed consent.

<table>
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<th>Characteristic</th>
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<tr>
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<tr>
<td>Primary tumor site</td>
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<td>Colon</td>
<td>136</td>
</tr>
<tr>
<td>Rectum</td>
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</tr>
<tr>
<td>Number of metastatic sites</td>
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</tr>
<tr>
<td>2</td>
<td>74</td>
</tr>
<tr>
<td>≥3</td>
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</tr>
<tr>
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<tr>
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</tr>
<tr>
<td>1</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>Liver replacement by tumor</td>
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</tr>
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</tr>
<tr>
<td>&lt;25%</td>
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</tr>
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</tr>
<tr>
<td>Previous chemotherapy for metastases</td>
<td></td>
</tr>
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<td>Yes: no</td>
<td>118:74</td>
</tr>
</tbody>
</table>

² Mean (range).
² 5-FU, 5-fluorouracil.

**Evaluation of the Rest/Activity Cycle**

Individual activity rhythms were measured noninvasively with a small-size wrist-worn piezoelectric accelerometer (Actigraph; Ambulatory Monitoring Inc., New York). The user-defined time interval for the count of wrist accelerations was 1 min. Patients were asked to wear the actigraph for at least three consecutive 24-h spans, which is the recommended duration for evaluating activity circadian rhythm (29). Each patient kept a diary for times of rising and retiring. Data were retrieved and analyzed with specific programs (Ambulatory Monitoring Inc.).

The circadian rhythm in activity (main evaluation criteria) was estimated by two parameters: autocorrelation coefficient at 24 h (r24), and a dichotomy index (I<0) comparing amounts of activity when in bed and out of bed. For the autocorrelation, if Xi is the measurement at time i, the correlation coefficient rXY between Xi and X(i+k) is computed for lags k, with k = 1–4320 min (72 h); the coefficient at 24:00 h (r24) can, in theory, range between −1 and 1. If there is a circadian variation, the correlation coefficient will increase around 24-h lags, and a more pronounced circadian rhythm will result in a higher coefficient at 24:00 h (Fig. 1a; Ref. 30). I<0 is the percentage of the activity counts measured when the patient is in bed that are inferior to the median of the activity counts measured when the patient is out of bed; thus I<0 quantifies the level of activity

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3 The abbreviations used are: PS, performance status; QoL, quality of life; CEA, carcinoembryonic antigen; r24, autocorrelation coefficient at 24 h; I<0, dichotomy index; EORTC, European Organization for Research and Treatment of Cancer; HADS, Hospital Anxiety and Depression Scale; CI, confidence interval.
3040 24-h Activity Rhythm Predicts for Cancer Survival

Circadian Rhythm Assessment for Blood-borne Variables

Circadian changes in cortisol and in WBC counts were used as secondary criteria. They were estimated from blood samples collected at 8:00 h and at 16:00 h for 2 consecutive days because the difference between values at these times was shown to be a reliable estimate of the amplitude of circadian rhythm in control subjects and in colorectal cancer patients (32).

QoL Assessment

QoL questionnaires were filled in by the patients before putting on the actigraph. A study investigator was available for questions about the study and how to fill in the forms.

QLQ-C30, from EORTC, is a 30-item questionnaire that incorporates five functional scales, eight symptom scales, and a global QoL scale (33, 34). The questions are formatted with either yes/no answers or with four-answer categories, except for the two questions on general QoL, which are to be answered on a scale numbered from 1 to 7. All calculations were performed after linearly transforming the scores to a 0–100 scale, according to EORTC guidelines (in EORTC QLQ-C30 scoring manual). Higher scores for the global QoL and functional scales represent better functioning, whereas higher scores on the symptom scales indicate a higher level of disturbance.

The HADS consists of seven items that evaluate anxiety and seven that aim at measuring depression; all questions are formatted with four-categories answers. Individual anxiety and depression scores range between 0 and 21 (35–37).

Statistical Analysis

Descriptive Statistics. Mean scores and SEs were calculated for all demographic, clinical rest/activity or other rhythm-related as well as QoL parameters. Normality of distributions was checked.

Primary Hypothesis. Each of the main evaluation criteria (r24 and I<0) was assigned to one of four categories according to quartiles, and the survival of patients with very low (<25% quartile), low (>25% and <50% quartile), high (>50% and <75% quartile), or very high (>75% quartile) rhythm parameters was estimated with the Kaplan-Meier method (38), with a comparison of the survival curves by the log-rank test. A regression analysis was conducted on survival time, measured from the date of activity rhythm recording, with the Cox proportional hazard model (39).

Secondary and Exploratory Hypotheses. Parametric or nonparametric (Kruskal-Wallis) ANOVAs were also used to analyze mean rhythm or QoL parameters as a function of categorical demographic and clinical characteristics. Possible associations between rhythm parameters, QoL scores, and continuous clinical parameters were tested with Spearman rank correlations. The influence of each demographic, clinical, or rest/activity-related parameter on maximum tumor response to treatment was assessed by single and multiple factors linear regression. Finally, the multivariate Cox model was used to determine which factors were jointly influential on survival (39).

RESULTS

Analysis of the Rest/Activity Cycle. The pattern of most activity recordings (actograms) ranged between the contrasted examples that are represented in Fig. 2. The three subjects on the left in Fig. 2 had a high mean activity level (Fig. 1b; Ref. 31). Mean activity was calculated for each patient and used as a secondary criteria.

Fig. 1 Example of an actigraphy recording and of the methods for its analysis. a. raw data, i.e., activity counts during 48 h as a function of time; b. formula for the dichotomy index I<0; c. autocorrelation function showing the autocorrelation coefficient (Y axis) calculated as a function of successive time lags.

Fig. 2. Examples of three different activity patterns recorded with the actigraph. A 24-h period of activity and rest.

b. I<0:

% values "in Bed" < M values "Out of Bed"

c. Time-lag for calculation (hours)

r24

during the rest span, as defined in the patient’s diary. This index can theoretically vary between 0 and 100%, and a high I<0 reflects a marked rest/activity rhythm (Fig. 1b; Ref. 31). Mean activity was calculated for each patient and used as a secondary criteria.
uated patients, with a median of 0.42 and a normal distribution. I<0 ranged from 49 to 100%, with a median at 97%. Mean activity ranged from 6 to 152 cpm; the median value was 96.

**Overall Treatment Efficacy.** Median survival was 13.2 months, with 31% of the patients alive at 2 years. Sixty-seven patients displayed an objective response (35%), among which 3 were complete. The disease was stabilized in 72 patients (37.5%) and progressed in 53 patients (27.5%).

**Influence of Rest/Activity Rhythms on Survival.** Marked circadian rhythms in activity, i.e., high $r_{24}$ ($P < 10^{-4}$) and high I<0 ($P < 10^{-4}$), predicted for longer survival in the univariate Cox analysis. For graphic purposes, each individual rhythm parameter was assigned to one of four categories according to 25% quartiles. After a 2-year follow-up, survival was 34% (95% CI, 26–43%) for the patients with $r_{24}$ in the three upper quartiles compared with 10% (95% CI, 1–20%) for those whose $r_{24}$ was in the lowest quartile (Fig. 3a). Similarly, 2-year survival was nearly 5-fold higher for patients with I<0 in both upper quartiles (38%; 95% CI, 27–49%) compared with those with I<0 in the lowest quartile (8%; 95% CI, 1–15%; Fig. 3b).

**Relation of Rest/Activity to Other Rhythm-related Factors.** The estimate of cortisol circadian rhythm was positively correlated to $r_{24}$ ($r = 0.16; P = 0.04$) but not to I<0 or mean activity. The mean cortisol concentration was higher in patients with low values for rest/activity parameters ($r_{24}$: $r = -0.17; P = 0.04$, I<0: $r = -0.24; P = 0.007$). Mean circadian changes in leukocytes were larger for patients with a high $r_{24}$ ($r = 0.23; P = 0.003$) or high I<0 ($r = 0.21; P = 0.009$). The rhythm estimate of cortisol was not correlated to that of leukocyte count.

**Correlations between Rest/Activity and QoL.** Global QoL and physical functioning scores, as measured by EORTC QLQ-C30, were positively correlated to circadian rest/activity rhythm but not to the mean activity level. Fatigue and appetite loss were associated with decreased circadian rhythm parameters and with diminished mean activity, whereas pain was correlated with only one of the rest/activity rhythm parameters (I<0). Patients’ self-rated sleep difficulties were not significantly correlated to either the rest/activity rhythm or to mean activity. From the HADS questionnaire, depression was associ-
Prognostic Factors of Tumor Response. Objective response rates differed significantly as a function of PS ($P < 10^{-5}$) and previous chemotherapy for metastases ($P = 0.04$) in the univariate analysis. This analysis also showed that the probability for achieving an objective response was significantly influenced by the rest/activity parameters $r_{24}$ ($P = 0.02$) and $I < O$ ($P < 10^{-4}$) as well as the circadian rhythm estimate for leukocyte count ($P = 0.006$). The cortisol rhythm estimate did not influence objective response.

In the multiple regression model, only PS ($P = 0.02$), circadian rhythm in WBC count ($P = 0.03$), and $I < O$ ($P < 10^{-4}$) were jointly influential on maximum response to treatment.

Global Survival Analysis. Univariate survival analysis was performed for all clinical, rhythm-related, and QoL variables. PS, number of metastatic sites, and previous treatment for metastatic disease were strongly related to survival. Patients with $<25\%$ liver involvement had a longer survival than those with more extensive liver involvement or those with extrahepatic metastases; the latter patients usually had lung metastases associated with either peritoneal or bone metastases. High levels of CA19.9 or CEA were associated with shorter survival (Table 4). In addition to both rest/activity rhythm parameters ($I < O$ and $r_{24}$), mean activity was significantly related to survival as well as the scores for global QoL physical functioning, fatigue, appetite loss, pain, and depression (Table 3). No significant prognostic value was established for cortisol or leukocyte rhythm estimates with regard to survival.

After univariate analysis, the multivariate Cox model was used to determine which factors were jointly influential on survival. A first multivariate model was built using only well-established clinical factors. When added one by one to this multivariate clinical model, the three parameters from actigraphy maintained independent prognostic value, whereas only four of the QoL scores did (Table 3). Finally, the best fitting clinical prognostic model included liver involvement ($>25\%$ versus $\leq 25\%$), number of metastatic sites, previous treatment for metastases, and PS (2 versus 0) jointly with the rest/activity circadian rhythm and mean activity (Table 4). Thus, the circadian rest/activity rhythm added significant prognostic information to the well-established clinical factors related to the tumor or to the patient’s general condition (40). This was also the case for mean activity, but to a lesser extent, as documented by the smaller relative risk associated with this parameter.

To further determine whether rest/activity parameters provided additional prognostic information to that already contained in PS, Cox analysis was also performed separately in the subsets of patients with PS = 0 or with PS = 1. Survival was still significantly influenced by $I < O$ in the subgroup of patients with PS = 0 and in patients with PS = 1 (Table 5).

**DISCUSSION**

By measuring the rest/activity cycle as a major circadian clock output, actigraphy provides a simple tool for evaluating circadian system function in cancer patients. Because wrist monitoring of activity is totally noninvasive, there is no restriction on its use in an ambulatory setting. Dense and reliable individual data could be collected, and a pertinent analysis of the
rest/activity rhythm was achieved by the robust parameters chosen herein: r24 estimated the strength of the circadian periodicity, and I<0 quantified abnormal peaks of activity during the rest span. This technique has allowed detection of alterations of the rest/activity circadian pattern, with wide interindividual variations, thus confirming previous observations (23, 31).

The rest/activity rhythm was a strong predictor of both tumor response and survival in patients with metastatic colorectal cancer. Each of the rest/activity-related variables provided additional prognostic information on patients’ maximum response to treatment and survival potential to that of well-known clinical characteristics, the secretion of cortisol may be directly influenced by tumor burden and spread, whereas the activity rhythm may reflect the global effect of the disease on the circadian clock function.

This result demonstrated that low rest/activity rhythm parameters did not merely reflect poor PS and further confirmed that the rest/activity rhythm was an independent prognostic factor.

Mean circadian changes in WBC counts were associated with activity rhythms, but the correlation was weak; this might account for the prognostic value of the circadian rhythm in WBC for response but not for survival. The estimate of the circadian rhythm in cortisol, another output variable of the circadian clock in some cancer patients. As documented by the association of cortisol mean concentration with poor-prognosis clinical characteristics, the secretion of cortisol may be directly influenced by tumor burden and spread, whereas the activity rhythm may reflect the global effect of the disease on the circadian clock function.

This study also documented the existence of a link between the rest/activity rhythm and the welfare of cancer patients. Marked rest/activity rhythms are associated with high functional scores and low symptom scores. This is not surprising because several variables evaluated in QoL questionnaires, such as locomotor activity, sleep, and psychomotor performance, are or-

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3044 24-h Activity Rhythm Predicts for Cancer Survival

Table 5 Prognostic multifactorial models of survival in patients with PS = 0 and PS = 1: Statistical significance of the rest/activity cycle parameters and the clinical prognostic factors

<table>
<thead>
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<th>Variable</th>
<th>Subgroup</th>
<th>Subgroup</th>
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<tr>
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<td>PS = 0 (n = 123)</td>
<td>PS = 1 (n = 55)</td>
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<tr>
<td>Rest/activity rhythm (I &lt; O)</td>
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<td>Liver involvement</td>
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<td>(0% versus ≥25%)</td>
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<td>NS</td>
</tr>
<tr>
<td>(&lt;25% versus ≥25%)</td>
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*Number of patients.

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