Sleep Medicine 16 (2015) 391–398

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Subjective sleep and overall survival in chemotherapy-naïve patients with metastatic colorectal cancer

Pasquale F. Innominato [a,b,*], David Spiegel [c,d], Ayhan Ulusakarya [a,b], Sylvie Giacchetti [b,e], Georg A. Bjarnason [f], Francis Lévi [a,b,g,h], Oxana Palesh [c,d]

[a] Assistance Publique – Hôpitaux de Paris, Department of Oncology, Paul Brousse Hospital, Villejuif, France
[b] INSERM, UMRS 776 'Rythmes Biologiques et Cancers', Villejuif, France
[c] Center for Stress and Health, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA
[d] Stanford Cancer Institute, Stanford, CA, USA
[e] Breast Diseases Unit, Department of Medical Oncology, Assistance Publique – Hôpitaux de Paris, St. Louis Hospital, Paris, France
[f] Division of Medical Oncology, Sunnybrook Odette Cancer Center, Toronto, Ontario, Canada
[g] Université Paris Sud 11, UMR-S0776, Orsay, France
[h] Cancer Chronotherapy Unit, Warwick Medical School, Warwick University, Coventry, Warwickshire, UK

ARTICLE INFO

Article history:
Received 17 August 2014
Received in revised form 5 October 2014
Accepted 9 October 2014
Available online 22 January 2015

Keywords:
Sleep
Colorectal cancer
Survival
Circadian
Chronotherapy
Time-dependent covariates

ABSTRACT

Backround: Sleep disorders are prevalent in patients with advanced cancer. Their impact on clinical outcomes is not well understood.
Methods: A post-hoc analysis was conducted in 361 chemo-naïve patients with metastatic colorectal cancer completing twice the EORTC QLQ-C30 questionnaire within a randomized international phase III trial. The study assessed the effect on overall survival (OS) of subjective sleep complaint, used as a normal or a time-dependent covariate (TDC), using a multivariate Cox proportional hazard model. Prognostic analysis was conducted on the whole study population and separately in each treatment arm (conventional FOLFOX2, or chronomodulated chronoFLO4).
Results: Sleep problems were reported by 202 patients (56%) at baseline and by 188 (52%) on treatment. Sleep problems at baseline were independently associated with a higher risk of earlier death (HR: 1.36; p = 0.011), progression (HR: 1.43; p = 0.002) and poor treatment response (RR: 0.58; p = 0.016). TDC analysis confirmed the independent prognostic effect of sleep problems on OS (HR: 1.37; p = 0.008), while on treatment this effect was only observed using univariate analysis. The negative prognostic value of sleep problems on OS at baseline, on treatment, and as a TDC was greatest on chronoFLO4 compared to FOLFOX2.
Conclusions: Subjective sleep problems are associated with poor clinical outcomes in metastatic colorectal cancer patients and affect chronotherapy effectiveness. There is a need for a well-tuned circadian timing system in order to increase chronotherapy activity. Prospective studies are needed for determining the impact of therapeutic approaches on sleep disorders upon quality of life and survival of cancer patients.

1. Introduction

Sleep problems are prevalent in cancer patients and survivors, with nearly two-thirds of patients reporting them [1–4]. However, relatively little is known about sleep disorders in colorectal cancer patients. In a study of 157 adults with colon or rectal cancer, sleep problems were reported by 35% of them, and higher levels of sleep problems predicted for more fatigue, together with more depression and poorer performance status [5]. In another small study involving 21 patients with colorectal cancer undergoing adjuvant chemotherapy, clinically significant sleep disturbances were observed [6]. Berger et al. also noted substantial evidence of circadian disruption in their sample, suggesting that patients diagnosed with these types of cancer experience lack of distinction between nighttime and daytime in their activities [6]. This phenomenon was previously described by patients with advanced cancers, where substantial amounts of time spent asleep during the day and awake during the night effectively blur the line between day and nighttime [7–9]. The observed association between altered rest–activity rhythm and subjectively reported sleep problems in two independent cohorts of patients with metastatic colorectal cancer [10,11] further supported the hypothesis that disruption of circadian rhythms in cancer patients plays a role in the occurrence of sleep problems.

* Corresponding author. INSERM U776 'Biological rhythms and cancer', Campus CNRS, Bat A 3ème étage, 7 rue Guy Moquet, 94801 Villejuif cedex, France. Tel.: +33 1 49 58 34 79; fax: +33 1 49 58 34 59.
E-mail address: pasquale.innominato@inserm.fr (P.F. Innominato).

http://dx.doi.org/10.1016/j.sleep.2014.10.022
1389-9457/

Evidence from several epidemiological studies suggests that chronic circadian disruption is carcinogenic and associated with an increased risk of many cancers, including colorectal cancer [12,13]. Sleep disorders have also been reported to be associated with numerous adverse psychiatric and health outcomes, including: neurocognitive, metabolic, endocrine, and immune effects; increased fatigue; decreased physical activity; drowsiness; anxiety; depression; and an increased perception of pain [14–16]. These data point to circadian disruption as a potential mechanism for sleep problems and the associated health risks.

Despite this scientific evidence and the common knowledge of adverse health being associated with disturbed sleep, data on large populations of cancer patients are lacking with regard to the effects of sleep problems on clinical outcomes. Nonetheless, other patient-reported symptoms have been more extensively studied and their importance as independent prognostic factors in various cancers, including advanced colorectal cancer, has been confirmed [1,17–22].

The present study examined the prognostic role of subjective sleep complaints, before and during chemotherapy, in patients diagnosed with metastatic colorectal cancer. Data were obtained from a randomized controlled trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) Chronotherapy Group.

2. Patients and methods

2.1. Study objective and design

The present clinical trial enrolled 564 patients, who were previously untreated for metastatic disease, from 36 centers in 10 countries between October 1998 and February 2002. A total of 282 patients were randomly assigned to one of the following treatment arms: FOLFOX2 or chronoFLO4 [23] (Fig. 1). Both regimens combined oxaliplatin, 5-fluorouracil, and leucovorin, administered with either a conventional, non-time-stipulated 2-day delivery (FOLFOX2), or with a chronomodulated, circadian-based infusion for four days (chronoFLO4). The description of these schedules, the patient inclusion and exclusion criteria, and the report of overall outcomes of the trial have been detailed elsewhere [23]. The study, which was approved by the EORTC protocol review committee and the ethics committee of each participating center, was conducted in compliance with the Helsinki declaration. All patients provided written informed consent.

2.2. Sleep assessment

Participants' subjective sleep was measured using the corresponding scale of a multidimensional questionnaire of HRQoL, the EORTC Quality of Life Questionnaire C30 (QLQ-C30) version 2.0 [24]. Assessments were performed at baseline (before chemotherapy start, but after a variable amount of time since initial cancer diagnosis and staging work-up) and during protocol chemotherapy (every fourth cycle of chemotherapy, about two months apart). The sleep score from EORTC QLQ-C30 was calculated using the recommended EORTC procedures [24] and involved the transformation of raw scores of increased severity into a linear scale ranging from 0 to 100. In particular, the EORTC QLQ-C30 questionnaire involves one straightforward question: '[During the past week] Have you had trouble sleeping?' It was considered that participants had no subjective sleep complaints if they answered 'not at all' (corresponding to 0 on the scale). The other values of the scale (ie, 33.3, 66.7 or 100, corresponding to 'a little', 'quite a bit' and 'very much', respectively) were considered as subjective reports of sleep problems.

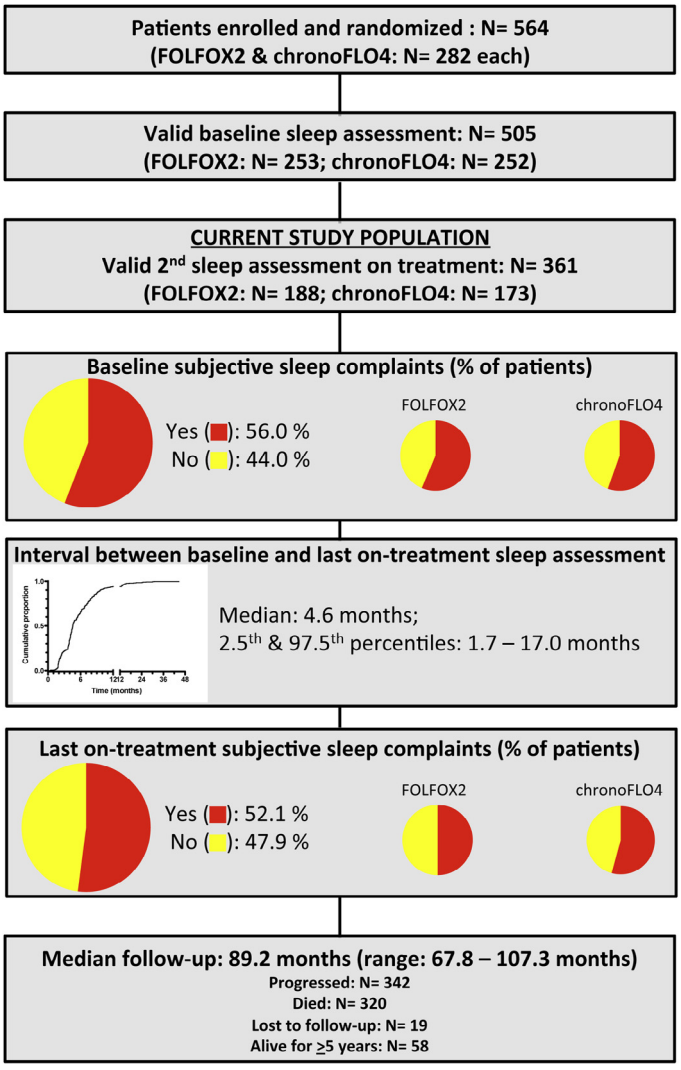

Fig. 1. Study flowchart.

2.3. Statistical analysis

The primary endpoint of the present study was the association between subjective sleep complaints and overall survival (OS). This association was explored by using sleep scores at baseline, while on treatment, and as time-dependent covariates (TDC). In each case, OS was measured from the date of completion of the corresponding questionnaire to the date of death (due to any cause). Participants still alive at the time of database locking were censored at the last date known to be alive. Similarly, time to progression (TTP) was calculated from the date of questionnaire completion until the date of disease progression or death, whichever occurred first.

Survival curves and probabilities were estimated using the Kaplan–Meier technique, and differences between survival curves were assessed using the log-rank test. The Cox proportional hazards regression model was used for both univariate and multivariate analyses of survival. For the prognostic analysis, the subjective sleep complaint was used either as a simple variable or as a time-dependent covariate. A multivariate prognostic model was then built, forcedly entering other possible prognostic factors. The added adjusting factors included: randomized treatment, age, sex, site of primary tumor, resection of primary tumor, Duke's stage at diagnosis, prior adjuvant chemotherapy, World Health Organization (WHO) performance status (PS) at baseline, number of metastatic