Temporal interrelationships among fatigue, circadian rhythm and depression in breast cancer patients undergoing chemotherapy treatment

Abstract Seventy-eight female breast cancer patients were assessed for fatigue, depression, overall mood, and circadian rhythm at their second and fourth on-study chemotherapy cycles as part of a larger study examining the efficacy of paroxetine in reducing chemotherapy-induced fatigue. The Multidimensional Assessment of Fatigue (MAF), the Fatigue Symptom Checklist (FSCL), the Center for Epidemiologic Studies-Depression (CES-D) questionnaire, the Hamilton Depression Inventory (HDI), and the Profile of Mood States (POMS) were completed by patients at home 7 days after each treatment to assess symptom severity. Circadian rhythm was assessed over a 72-h period with the Mini-Motionlogger Actigraph (Ambulatory Monitoring, Ardsley, NY), starting 6 days after treatment. Daily patterns of sleep and activity were compared across the 3-day period by autocorrelation analyses to calculate a circadian rhythm score for each patient, with higher scores associated with lower disruption. Comparisons of fatigue, depression, and mood with patient circadian rhythm measures taken after the second cycle indicate that all five paper and pencil measures correlated well with the measure of circadian rhythm (all $r_{\text{partial}} < -0.30$, all $P < 0.05$). Changes in the fatigue, depression and mood measures from the second on-study treatment to the fourth were significantly correlated with concurrent changes in circadian rhythm (MAF $r = -0.31$; $P = 0.04$; FSCL $r = -0.30$; $P = 0.04$; CES-D $r = -0.39$; $P = 0.008$; HDI $r = -0.34$; $P = 0.03$; POMS $r = -0.40$; $P = 0.007$). These findings provide evidence that circadian rhythm disruption is involved in the experience of fatigue and depression in cancer patients.

Keywords Fatigue · Depression · Circadian rhythm · Cancer treatments · Side-effect
participate in leisure activities, impede concentration, and diminish the ability to work [6, 11, 12]. Fatigue can significantly reduce a patient’s ability to perform the activities of daily living. High fatigue may also force patients into a dependent position of having to rely on others for home management, transportation, and even simple aspects of self-care activities, such as preparing food or bathing.

Circadian alterations and fatigue

A role has been suggested for circadian rhythms, or disruption of them, in fatigue related to chemotherapy [2, 42]. Circadian rhythms are endogenous, genetically based, physiological patterns that run on an approximately 24-h cycle. They modulate several biological functions, including body temperature, cortisol, melatonin and growth hormone secretion, and REM sleep [18, 30, 38, 41]. These rhythms can be altered by environmental factors, such as light and dark alterations. Desynchronization of circadian rhythms results in symptoms such as sleep disorders, trouble concentrating, irritability, depression, lightheadedness, and loss of appetite [16].

Evidence from experimental tumor models and from cancer patients shows that cancer may also alter circadian rhythms [9, 18, 19, 35, 36]. For example, Mormont et al. [20] found large circadian variation in measures of serum cortisol concentrations in patients with colorectal cancer. Average peak–trough differences were significantly smaller (30%) in patients with colorectal or ovarian cancer than in healthy controls. Relatedly, Ronco and Halberg [33] found that melatonin production, which is involved in the control of sleep, is more strongly correlated with the circadian pattern in healthy individuals than in women with breast cancer.

One method of studying the relationship between these 24-h biological rhythms and fatigue is by monitoring activity levels. This may be done through the use of an actigraph, a motion-sensing device approximately the size of a man’s watch that is worn on the wrist and is comprised of an accelerometer, a microprocessor, and 32 K of retrievable memory. Actigraphy is a simple noninvasive method of measuring levels of daytime and nighttime activity and can be used for accurate estimation of the amounts of both day- and nighttime sleep. In addition, activity patterns over several consecutive days can be analyzed with autocorrelational techniques to provide estimates of circadian rhythms [14, 40].

Using actigraphy, a negative relationship between fatigue and activity levels during the day and a positive relationship between fatigue and restless sleep at night has been found in cancer patients [2, 19]. Mormont’s group [18] also reported markedly lower general activity levels in colorectal cancer patients during the day and higher activity levels during the night than in a matched group of controls. In addition, the difference between daytime and nighttime activity levels in cancer patients was smaller than in the matched group of controls. Furthermore, Mormont found the circadian rhythm of activity and rest to be altered in the group of colorectal cancer patients but not in the control group. She concluded that cancer patients might have a disruption in their activity circadian rhythm cycle.

This present study examines the temporal interrelationships among fatigue, circadian rhythms, and depression in breast cancer patients undergoing treatment with chemotherapy. We examined depression as a variable of interest in its own right and also because of its strong association with fatigue [3, 5, 13, 26]. Although the nature of the relationship between these two phenomena is not fully understood, one study found fatigue led to depression more than depression resulted in fatigue [43]. There is substantial evidence linking depression with alterations in the circadian rhythms of various physiological parameters and activity levels [4, 10, 15, 45].

Materials and methods

Procedures

Data were collected as part of a double blind, placebo-controlled clinical trial examining the efficacy of an antidepressant medication in attenuating or preventing the development of fatigue in women during chemotherapy treatment for breast cancer. Patients were randomized to receive either 20 mg paroxetine (Paxil) or a placebo of identical appearance daily. Any patient receiving chemotherapy at any time in her/his course of treatment was potentially eligible if she/he was scheduled to receive at least four additional cycles of chemotherapy (any regimen) without concurrent radiation therapy or interferon. Radiation therapy (typically 30 treatments) sandwiched between cycles of chemotherapy was allowed and counted as a treatment cycle. Changes in chemotherapy doses or regimens were also allowed. Treatment cycles were a minimum of 2 weeks apart. The study medication was begun minimum of 2 weeks apart. The study medication was begun 7 days after the first on-study treatment and concluded 7 days after the fourth on-study treatment. Patients taking psychotropic medication or who had a history of psychiatric or certain neurologic diagnoses were not eligible to participate. Study subjects were patients at a university medical center and two affiliated hospitals. The Institutional Review Boards of each participating institution approved the study, and all patients gave written informed consent.

Outcome measures

Patients were assessed using the Karnofsky Performance Scale at study entry and completed measures of fatigue, depression, and overall mood following each of the four on-study chemotherapy treatments. Measures were completed at home on the 7th day after each treatment. A reminder telephone call was made to patients on the day the questionnaires were to be completed. Patient activity was sampled by actigraphy for a continuous 72-h period during the 6th, 7th and 8th days after the second and fourth on-study treatments with the Mini-Motionlogger Actigraph (Ambulatory Monitoring). Motion, or lack of motion as the case might be, was recorded six times a minute during this time period. The motion