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Feasibility of a Randomized Controlled Trial of Light Therapy in Cancer Patients with Insomnia

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Abstract

Purpose: The primary objective of our study was to compare bright light therapy versus dim red light for global sleep quality in palliative care patients with cancer.

Methods: The study was designed as a randomized, double blind, placebo controlled trial. Patients initiated blinded phase, either daily bright light versus red light placebo, from day 1 to day 14, then proceeded to an open label phase between day 15 to day 28.

Results: Of the 319 outpatients assessed for eligibility, 97 patients (30%) fulfilled criteria for the study. Of the 97 patients, only 12 patients (12%) enrolled in the study with the majority unwilling to participate or reported a lack of interest in light therapy. Only 4 patients (33%) completed the trial to the primary endpoint at 2 weeks.

Conclusion: At our institution, a randomized controlled trial examining bright light therapy, a potentially safe and effective non-pharmacological approach to treat sleep disturbances, was not feasible for palliative care patients with cancer. Future studies should be tailored to advanced cancer patients who are often frail and have a high symptom burden, incorporate alternative trial designs such as randomization without a placebo arm, and consider integration of home visits or assessment by phone calls to lessen the burden of participation in a clinical trial.

Keywords: Light therapy; Insomnia; Sleep disturbances; Cancer

Introduction

For cancer patients, sleep provides respite from physical and psychological distress, [1] restores a sense well-being [2,3] and maintains cognitive function [4]. Insomnia has a negative impact on quality of life [5], ability to engage in work or recreational activities, and is associated with neuro-endocrine abnormalities [6,7].

The prevalence of sleep disturbance in cancer patients ranges from 24% to 95% [8-14]. Insomnia affects about 70% of hospice patients, with frequent waking being the most common problem reported [15]. Hypersomnolence, excessive daytime sleepiness, is also common in cancer patients and frequently associated with opioids.

Patients with insomnia frequently develop tolerance to hypnotics and their use may result in fragmented sleep and dependence [16]. Undesirable side effects of hypnotics include day-time sedation, delirium, fatigue, and respiratory depression. A recent study reported that hypnotic use was associated with a greater than threefold increased risk for death even when patients were prescribed less than 18 pills per year [17]. In cancer patients, 23% of the populations were utilizing hypnotics and their use was associated with older age, increased stress and anxiety, greater use of opioids, and history or current chemotherapy treatment [18].

One promising non-pharmacologic treatment for insomnia is bright light therapy (BLT). BLT has been studied in institutionalized elderly patients [19-23] and adolescents with delayed sleep phase disorder. [24] In breast cancer patients receiving chemotherapy, stage I-III, BLT was shown to prevent an increase in total fatigue scores [25].

Advanced cancer patients often have altered sleep patterns resulting in disruptions in their circadian rhythm [26,27] which may be restored with BLT. The primary objective of our study was to compare BLT with dim red light on global sleep quality in advanced cancer patients. We hypothesized that BLT was more effective than dim red light in improving sleep disturbances.

Methods

Participants

We planned to recruit a total of 152 patients for the two arms (i.e. 76 per arm) at a single site, MD Anderson Cancer Center (MDACC) – Supportive Care Clinic. Patients were eligible if they had advanced cancer with an average sleep disturbance rating of ≥ 4 out of 10, as measured by the Edmonton Symptoms Assessment Scale (ESAS), [28] with a rating of 0 having no problems sleeping and 10 being severe difficulties sleeping for at least one week; age 18 or greater; Karnofsky performance status score of ≥40; agreeable for follow-up visits at MDACC; and English speaking. Patients were excluded if they had congenital blindness or acquired blindness; history of retinal disease; current diagnosis of major depression or generalized anxiety disorder; received light therapy in the past; currently on amiodarone, thiazide diuretics or EGFR inhibitors (erlotinib, gefitinib, cetuximab,

panitumumab); receiving UVA/UVB therapy; diagnosis of obstructive sleep apnea or narcolepsy; and patients with >2 hours of direct exposure to outdoor natural light per day. Patients who were using pain medications and/or had a history of taking any hypnotics for sleep disturbance on a regular or "as needed" (PRN) basis, but still rate insomnia ≥ 4 on scale ranging from 0 to 10, were eligible.

Study design

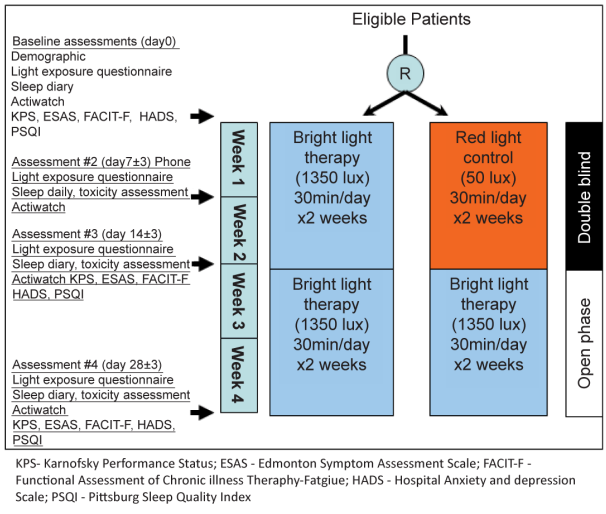

Figure 1: The study was a randomized, double-blind, placebo-controlled trial.

Patients initiated the blinded phase of study intervention (i.e. daily bright light or red light) from day 1 to day 14 ± 3, then proceeded to an open label phase and received daily bright light between day 15 ± 3 and day 28 ± 3.

Study intervention

The active treatment arm received BLT via a Litebook device (The Litebook Company Ltd., Alberta, Canada). The Litebook device, a small and lightweight box, consists of 60 LEDs with spectral emission with a peak at approximately 464 nm and fluorescent phosphors which provide a broader, secondary spectral peak near 564 nm.

The control, previously used in randomized trials of BLT, is a red light device was also produced by Litebook and was identical in appearance and dimensions, with the exception that it emits light at a wavelength of 680nm (i.e. red light) and at an intensity of 50 lux [29-31]. Subjects were instructed on the use of the Litebook devices with regard to proper positioning, duration, and start of therapy - 30 minutes each morning, within 2 hours of awakening on a daily basis.

A randomization list was prepared by our study biostatistician in advance of trial initiation. Once enrolled, study participants were issued an active or control treatment device by a research staff (different from the blinded staff who performed study assessments).

Outcomes

Patient demographics and performance status, as well as Karnofsky Perfomance Scale, were recorded. A light exposure diary, the participants were asked to transcribe their daily indoor and outdoor activities with duration at baseline, day 7, 14, and 28 (Figure 1). In addition, a sleep diary, a subjective tool utilized in a number of studies on sleep disorders and in general practices [32], was also recorded.

The following assessments were conducted at baseline, day 14, and day 28 (Figure 1).

The Edmonton Symptom Assessment Scale (ESAS) measures the patient's response to 9 common symptoms in the past 24 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep problems) and the feeling of well-being [28].

The Pittsburgh Sleep Questionnaire Inventory (PSQI), a validated tool for insomnia, is an effective instrument for measuring the quality and patterns of sleep [33].

The Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-F) subscale has been used primarily in cancer patients to measure fatigue; [34,35]. It consists of 27 quality-of-life questions which cover the following domains: physical, social, emotional, and functional. The Hospital Anxiety and Depression Scale (HADS) is a brief, self-administered, and widely used screening tool to measure psychological distress in patients. It is sensitive to change both during the course of disease and in response to medical and psychological interventions [36,37].

Continuous assessment of activity was measured by actigrapy (Actiwatch 64 IPX7 portable recorder; Mini Mitter Company, Inc. A Respironics, Inc., OR, USA) which is a small wrist-worn device optimized for highly effective sleep-wake inference from wrist activity which has been previously validated [38,39]. Patients were instructed to wear the actigraphs throughout the study period and remove them during bathing.

Results

Of the three hundred and nineteen patients assessed for eligibility, only 97 patients (30.4%) fulfilled inclusion and exclusion criteria. The majority of patients excluded from the study were due to treatment with a medication with which light exposure was contraindicated; mainly phase 1 therapy with EGFR inhibitors (erlotinib, gefitinib, cetuximab, panitumumab). Seventy four patients with difficulty sleeping did not rate insomnia greater than 4 on the ESAS. Ten patients were excluded secondary to depression.

Of the 97 patients who were eligible, very few patients, 12 (12.4%), enrolled in the study with the majority of patients, 58 (59.8%), unwilling to participate in the trial due to the need to return for follow-up visits. Another 27 patients (27.8%) were not interested in BLT.

Of the 12 patients enrolled, only 4 (33.3%) were able to complete the primary endpoint at 2 weeks. Various reasons for patients dropping out of the trial were provided and included patient's clinical health declining, initiation of phase1 treatment with a contraindication to light exposure, preference for natural light exposure, and patient or family members lack of interest in enrollment (Figure 2).

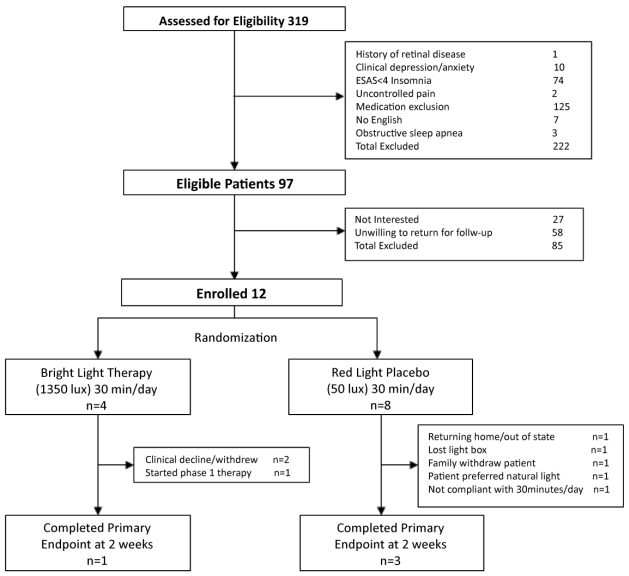

Figure 2: Outlines accrual information, participants who completed the study to primary endpoint at 2 weeks, and the reason for dropping out of the trial.

Discussion

Sleep disturbances are common in patients with cancer. Despite the ease of use and limited toxicity [40], a randomized controlled trial evaluating BLT in advanced cancer patients at our institution was not feasible secondary to poor accrual and a high attrition rate. Even if the study were to continue, the high percentage of non-eligible patients and low completion rate would limit generalizability.

Using a similar research design, Ancoli-Israel and colleagues completed a study of BLT which included 39 patients with stage I-III newly diagnosed breast cancer undergoing chemotherapy; authors reported that light therapy prevented deterioration in total fatigue scores [25]. However, studies of patients with early stage disease may not be applicable in patients with advanced disease receiving palliative care secondary to their frail condition with increased symptom burden, intensity of other treatment modalities (i.e. chemotherapy, radiation treatment), and increased susceptibility to side effects. In our study, patients, despite being functional, were in the late stages of their disease trajectory. In the palliative care setting, it is not uncommon for eligible patients decline to enroll in studies, which has been reported to exceed 50 percent [41-43].

Barriers to enroll in BLT study included the large number of patients receiving phase 1 therapy with epidermal growth factor receptor (EGFR) inhibitors. Treatment with EGFR inhibitors may lead to a skin reaction which can be exacerbated by sun exposure [44] and was an exclusion criteria. In addition, the study was randomized, Figure 1, with a 2 week placebo controlled phase prior to open label treatment which may have discouraged patient participation. As more patients have knowledge and access to BLT, the ability to distinguish BLT from placebo makes blinded randomization problematic. Also, the need for return visits to complete assessments for the trial discouraged potential participants, and in future studies, follow-up assessments by phone call should be considered.

Other factors contributing to the failure of the study include the possible lack of enthusiasm by physicians and also, arguably, a preference for patients for pharmaceutical intervention for their sleep disturbances. A limitation of the current study is the lack of specific detailed information for why patients were not interested in participation which may due to fear of side effects, inability to comply with daily use, or cancer patients may have felt that BLT was inadequate to alleviate their symptoms. Enlight of a recent study which reported an increased mortality associated with the use of hypnotics in cancer and non-cancer patients [17], future studies may have to highlight the risks of hypnotics for the treatment of insomnia in order to persuade patients to use a safer non-pharmacological intervention.

Conclusion

Patients with advanced cancer in a tertiary cancer center lacked interest in receiving BLT for symptoms of insomnia. Of those that choose to enroll in a randomized control trial, therapy was not tolerated resulting in a high attrition rate. Future studies should be tailored to advanced cancer patients who are often frail and have a high symptom burden, incorporate alternative trial designs such as randomization without a placebo arm, and consider integration of home visits or assessment by phone calls to lessen the burden of participation in a clinical trial.

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