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The survival and quality of life benefits of melatonin when administered to cancer patients at the optimal time of day

Submission date
30/03/2015

Recruitment status
No longer recruiting

Registration date
07/05/2015

Overall study status
Completed

Last Edited
07/05/2015

Condition category
Cancer

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims

The molecular clocks that synchronize and coordinate biological processes that keep us alive are called circadian. Circadian clocks control the most basic cellular metabolic processes to the complex emotional and cognitive functioning of the brain that give humans our sense of wellbeing. We directly experience circadian clock function when we become sleepy and the time we awake. Circadian clocks regulate nearly all clinically important biological functions such as heart rate, blood pressure, body temperature, pain, renal (kidney) function, and many more physiological variables used by physicians to determine if we are healthy or sick. During the past thirty years, we have discovered that the continuous availability of nocturnal (night-time) light and the avoidance of daytime sunlight can disrupt our circadian rhythms. The reason for this disruption is that circadian clocks use light as a key cue to synchronize our bodily rhythms, especially during those periods in the day when we sleep. Nowadays, many working adults have circadian rhythms that are not properly synchronized to the solar day. They therefore need to use alarm clocks to awaken in the morning on their work days while they catch up on their much needed sleep by sleeping much later on their work free days. Circadian rhythms are particularly severely disrupted in workers who do rotating shift work. Although shift work is needed to achieve the economic goals of our economy; shift workers have been participants in a gigantic uncontrolled public health experiment on the biological and health effects on the chronic distortions of their circadian rhythms. We now know that working the night shift leads to a number of health effects, which range from insomnia, daytime sleepiness, fatigue, depression, obesity, hypertension (high blood pressure),cardiovascular (for example, heart) disease and surprisingly, significantly increased risk for a number of cancers. The regulatory agency involved in identifying human carcinogens (a substance or environmental factor thought to increase the risk of cancer) has categorized shift work as a ‘probable carcinogen’. Tumor biologists have discovered that many of the molecules that regulate the clock are also be involved in the development of cancer. There is strong evidence showing shift work causes or increases the development of cancer and that the emergence and progression of cancer causes an ever greater distortion of the host’s circadian rhythms. Consequently, cancer patients develop the symptoms of a distorted circadian rhythm— insomnia, daytime fatigue and sleepiness, and depression which makes the life of many of these patients miserable. In addition, anti-cancer

therapy often does not work in patients with the worst or failing circadian function; so cancer patients with a dysfunctional circadian physiology have shorter than expected lifespans while experiencing symptoms that describe a poor quality of life. One of the outputs of the circadian clock is melatonin. The circadian daily variation in the amount of melatonin (concentration) is a marker of an individual's health. In young healthy adults, the serum melatonin levels surge in the early evening hours, peak in the middle of the night, and decline as dawn approaches. There is a gradual loss in melatonin's serum nocturnal surge as humans' age but in patients with advanced cancer, there is very little or no nocturnal surge in melatonin serum levels. The nocturnal surge of melatonin promotes high quality sleep and is tightly linked to the nocturnal release of growth hormone, insulin like growth factors, and other agents associated with tissue repair, maintenance, and self-regeneration. The loss of biological capacity for tissue repair and regeneration compromises the cancer patient's ability to repair the damage caused by conventional chemotherapy and radiotherapy. Most cancer patients have a diminished capacity for self-repair, and therefore not benefit as much as they should from conventional chemotherapy or radiotherapy. Here, we want to investigate whether a pill containing 20mg of melatonin can restore the circadian function of a patient with advanced cancer and find out when in the day the pill should be given.

Who can participate?
Adults with advanced lung cancer.

What does the study involve?
Participants are randomly allocated into one of four groups. Those in group 1 are given 20mg of melatonin in the morning. Those in group 2 are given 20mg of melatonin in the evening. Those in group 3 are given a placebo to take in the morning. Those in group four are given a placebo to take in the evening.

What are the possible benefits and risks of participating?
When this clinical trial was being designed there were several publications that investigated the toxicity of melatonin among patients with metastatic disease. In these investigations patients were given doses up to 750 mg/m2 with no recorded grade III toxic event. Overall the clinical community consensus is that melatonin can be safely given to people with metastatic cancer. In addition, these early studies indicated that melatonin had a mild anti-tumor effect as a benefit.

Where is the study run from?
The Cancer Treatment Centers of America Midwestern Regional Medical Center, Illinois (USA) and the WJB Dorn Veterans Medical Center, South Carolina (USA)

When is the study starting and how long is it expected to run for?
June 2001 to April 2006

Who is funding the study?
1. The Gateway for Cancer Research (USA)
2. National Cancer Institute (USA)
3. Life Extension Foundation (USA)

Who is the main contact?
1. Dr Bruce Steinert (public)
2. Dr James Grutsch (scientific)

Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CTCA 01-07

Study information

Scientific Title
A Multi-Center Randomized, Double-Blind, Trial Evaluating the Chronotherapeutic Role of Melatonin in the Treatment of Stage IIIB and IV Non-Small Cell Lung Carcinoma

Study objectives
This multi-center trial will evaluate the chronotherapeutic role of melatonin in the treatment of stage III and IV non-small cell lung cancer. The design of the clinical trial will address the following specific aims in patients with stage III and IV non-small cell lung cancer who are undergoing chemotherapy:

1. Determine what fraction of patients with advanced lung cancer suffer abnormalities of their circadian activity/rest rhythm
2. Evaluate whether the administration of exogenous melatonin will, at the appropriate circadian time, induce it's known biological responses of lowered body temperature and sleep consolidation
3. Evaluate whether the administration of exogenous melatonin at the appropriate circadian time will restore and maintain the circadian activity/rest rhythms of patients with advanced lung cancer undergoing chemotherapy
4. Measure the bioavailability of exogenous melatonin among patients undergoing chemotherapy
5. Determine whether appropriately timed melatonin therapy diminishes the toxicity of chemotherapy by a clinically significant level
6. Determine whether appropriately timed melatonin therapy improves health-related quality of life by a statistically significant level
7. Assess whether appropriately timed melatonin therapy diminishes patient fatigue by a statistically significant level
8. Determine whether appropriately timed melatonin therapy induces a statistically higher prevalence of tumor response and longer progression-free survival

Ethics approval required
Old ethics approval format

Ethics approval(s)
The institutional review boards of Cancer Treatment Centers of America (CTCA) at Midwestern Regional Medical Center (MRMC), Zion, Illinois, USA, 03/08/2001, ref: CTCA 01-07.

Study design
Interventional

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
The affects of adjuvant melatonin on the outcomes of stage III and IV non small cell lung cancer patients

Interventions
Chronotherapeutic administration of melatonin in patients undergoing chemotherapy
Participants are randomly allocated into one of three groups:

Group 1: was placebo at 8 AM and placebo at 8 PM
Group 2: was melatonin 20mg at 8 AM and placebo at 8 PM
Group 3: was placebo at 8 AM and melatonin 20mg at 8 PM
Patients self administered their placebo or melatonin drug daily while on study

All patients were treated with cytotoxic chemotherapy: cisplatin 25mg/m2/day (IV infusion over 3 days) followed by etoposide 100mg/m2/day m2/day (IV infusion over 3 hours over these same three days). Therapy was repeated every 28 days. Response to therapy was evaluated clinically and radiologically every third cycle. Treatment was continued until progression of the diseases (PD), development of unacceptable toxicity, patient withdrawal, or completion of six cycles of their planned treatment. Further therapy after PD was permitted in the protocol when indicated in the judgment of the attending oncologist. Dose of chemotherapy was unaltered if patients recovery WBC counts were greater than 4,000 and platelet levels were over 100,000. If levels failed to meet these cut-offs, chemotherapy was either delayed for up to two weeks or the dose of chemotherapy was reduced by 25%. Patients who stopped chemotherapy remained on melatonin/placebo therapy and continued to be evaluated every three months until progression.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Melatonin

Primary outcome measure
The following outcome measures were collected at baseline before the administration of chemotherapy and before the administration of the third treatment cycle.
1. Sleep quality: measured using the Pittsburgh Sleep Quality Index
2. Quality of life: measured using the EORTC QLQ-C30 which measures patient functioning and symptom burden and the Ferrans and Powers QLI which measures an individual's level of satisfaction with the human activities that give meaning and pleasure to life
3. Tumor response: was measured using the RECIST criteria
4. Circadian activity/rest cycle: measured using actigraphy devices supplied by Ambulatory Monitoring, Inc. Data was collected the week prior to treatment at the VA at baseline and three month followup; the baseline MRMC data was collected inpatient and as outpatients at the three month followup.
5. Survival data: collected on all patients until they died.

Secondary outcome measures
1. Determine what fraction of patients with advanced lung cancer suffer abnormalities of their circadian activity/rest rhythm
2. Evaluate whether the administration of exogenous melatonin will, at the appropriate circadian time, induce it's known biological responses of lowered body temperature and sleep consolidation

Overall study start date
05/06/2002

Completion date

04/04/2006

Eligibility

Key inclusion criteria
Patients with a primary histologic diagnosis of Stage IIIB-IV non-small cell lung cancer, with either bidimensionally measurable or evaluable unresectable disease including histologically positive ascites and histologically positive pleural effusion.
1. Patients with ECOG performance status of 0,1,2
2. Patients who sign Informed Consent indicating that they are aware of the investigational nature of the study and the randomized study design
3. Patients with chemo-failures from one prior regimen are acceptable
4. Patients must agree to either:
4.1. Comply strictly with the CTCA Nutrition 5-Pak Supplement regimen provided throughout entire course of study
4.2. Consume no additional nutritional supplements outside of the CTCA Nutrition 5-Pak. (Clarification: Homeopathic remedies, therapeutic touch, reiki, massage and biofeedback are acceptable adjuvant natural therapies. No other biologically based therapies are allowed)
5. In the event that patients are on melatonin prior to study, a two-week washout period will be implemented before the initiation of therapy
6. Concurrent Radiation Therapy is allowed only for patients who initially present with an acute comorbidity requiring it (e.g. impending pathologic fracture, superior vena cava syndrome, etc.) The reason for concurrent XRT should be clearly documented

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
90

Key exclusion criteria
1. Presence of any serious medical condition with which the administration of study chemotherapeutic agents is contraindicated; Inadequate renal function with serum creatinine > 2.5; Inadequate hepatic function with bilirubin > 2.0 mg/dl; Abnormal baseline MUGA of <50% ejection fraction; Uncontrolled hypertension; uncontrolled arrhythmia; uncontrolled angina; carcinomatous meningitis; uncontrolled infection; or severely abnormal PFT’s (DLCO < 60%)
2. Primary diagnosis of any malignancy (ies) including, but not limited to: Small Cell Lung Cancer, Neuroendocrine carcinoma, sarcomas, and benign adenomas
3. Patients with a history of brain metastases
4. Women who are pregnant or women of childbearing potential who refuses to use prophylaxis against pregnancy while receiving chemotherapy regimens
5. Use of beta blockers in the evening (which interferes with pineal melatonin synthesis); if patient is currently on these medications, appropriate a.m. alternatives will be implemented prior to randomization
6. Any prior treatment failure with Cisplatin or VP16

7. Unwillingness to comply with standard nutritional 5-pak supplement regimen and not consume any nutritional supplements outside of the nutrition 5-pak

Date of first enrolment
06/06/2001

Date of final enrolment
04/04/2006

Locations

Countries of recruitment
United States of America

Study participating centre
Cancer Treatment Centers of America Midwestern Regional Medical Center
Zion, Illinois
United States of America
IL 60099

Study participating centre
WJB Dorn Veterans Medical Center
Columbia, South Carolina
United States of America
SC 29209

Sponsor information

Organisation
Cancer Treatment Centers of America®

Sponsor details
2520 Elisha Ave
Zion, Il
United States of America
60091

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/045ns1x37

Funder(s)

Funder type
Charity

Funder Name
The Gateway for Cancer Research (USA)

Funder Name
National Cancer Institute

Alternative Name(s)
Instituto Nacional del Cáncer, National Cancer Institute at the National Institutes of Health, Instituto Nacional del Cáncer de los Institutos Nacionales de la Salud, NCI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Funder Name
Life Extension Foundation (USA)

Results and Publications

Publication and dissemination plan
As soon as this trial becomes registered we will immediately submit a paper describing the relationship between the chronotherapeutic administration of melatonin with patient survival and tumor response. Several months later a second paper will report on the relationships between chronotherapeutic administration of melatonin and the patient's actigraphy results.

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		28/11/2005		Yes	No
Results article	Psychooncology. Feb;19(2):180-9.	01/02/2010		Yes	No
Results article	J Circadian Rhythms. May 18;9:4.	18/05/2011		Yes	No
Results article	BMC Cancer. May 23;11:193.	23/05/2011		Yes	No