Melatonin Supplementation for Cancer-Related Fatigue in Patients Receiving Radiotherapy: A Double Blind Placebo-Controlled Trial

MCC-12-08248
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12/10/2021

Title: Melatonin supplementation for cancer-related fatigue in patients receiving radiotherapy: A double-blind placebo-controlled trial

MCC Protocol #: MCC-12-08248 [redacted]

Sponsor-Investigator:
Alfredo Urdaneta, MD

[redacted]

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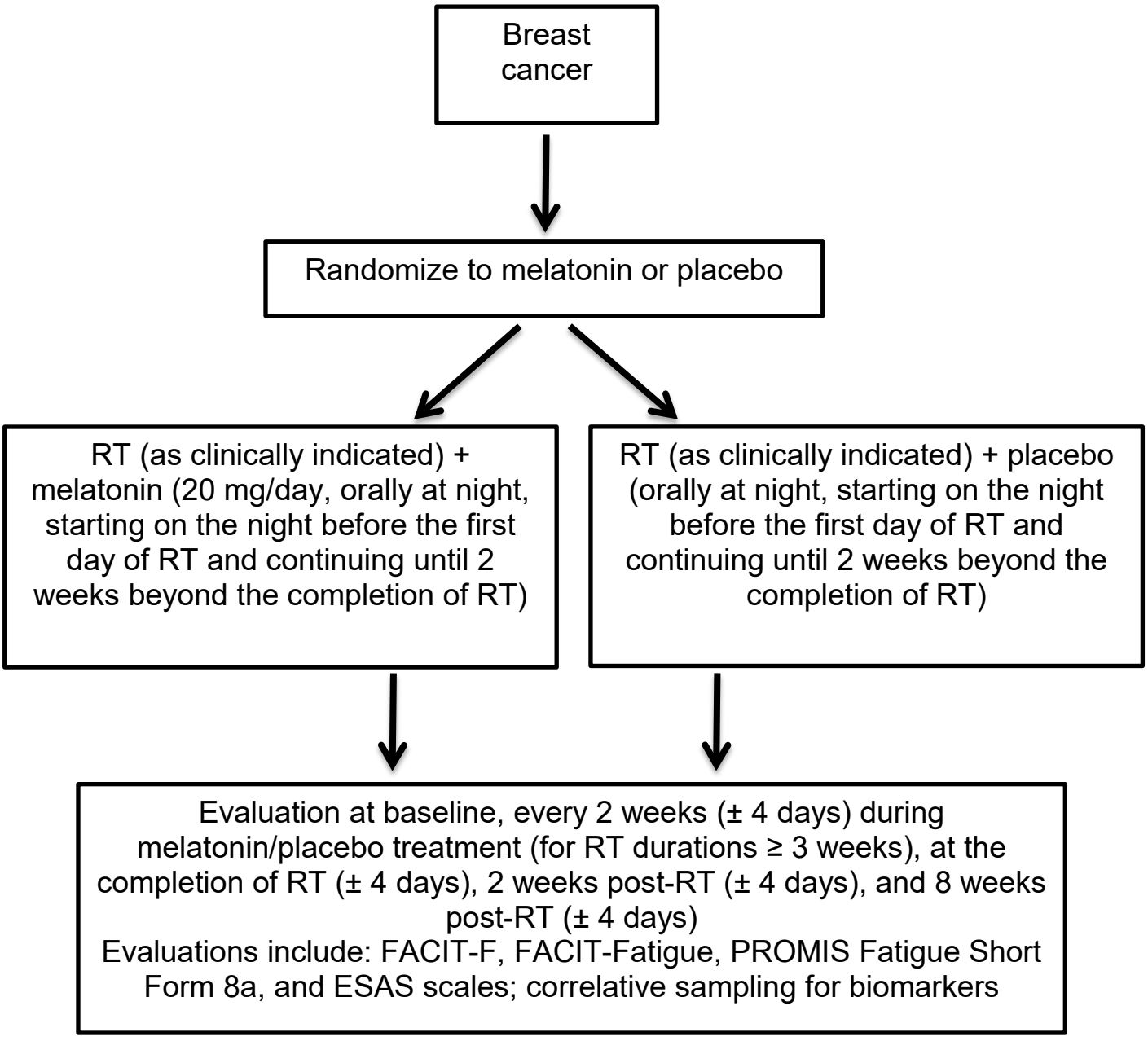
PROTOCOL SUMMARY

Title:	Melatonin supplementation for cancer-related fatigue in patients receiving radiotherapy: A double-blind placebo-controlled trial
Protocol Number:	MCC-12-08248
IND Sponsor:	Alfredo Urdaneta, MD
Sponsor-Investigator:	Alfredo Urdaneta, MD
Study Sites:	[redacted]
Clinical Trial Phase:	Phase 3
Study Disease:	Breast cancer
Main Eligibility Criteria:	Ambulatory outpatients with breast cancer to be treated with radiation therapy for curative intent; women ≥18 years of age; ECOG performance status <3.
Primary Objectives:	To determine whether the average increase in fatigue (as measured by the FACIT-Fatigue subscale) from baseline to completion of RT is different in those patients who received melatonin than in those who received placebo.
Secondary Objectives:	To determine whether the average increase in health-related quality of life (HRQOL) from baseline to completion of RT is greater in those patients who received melatonin than in those who received placebo. To determine whether the average increase in fatigue from baseline until (i) 2 weeks and (ii) 8 weeks after completion of RT is less in those patients who received melatonin than in those who received placebo. To determine whether the average increase in symptoms from baseline until completion of RT is less in those patients who received melatonin than in those who received placebo. To determine whether the average increase in fatigue (as measured by the PROMIS Fatigue-Short Form 8a) from baseline to completion of RT is less in those patients who received melatonin than in those who received placebo. To describe the level of agreement in reported fatigue scores when 2 different survey instruments are used to measure fatigue. To determine whether patients receiving melatonin have fewer hospital admissions, emergency center visits, and medical days off work than patients receiving placebo.

Endpoints:	The primary endpoint will use a comparison of FACIT-Fatigue subscale scores obtained at baseline and at the completion of RT. The secondary endpoints will use a comparison of FACIT-F scores obtained at baseline until (i) 2 weeks and (ii) 8 weeks after completion of RT. ESAS scores will be compared at baseline and at the completion of RT. A comparison of the PROMIS Fatigue-Short Form 8a scores obtained at baseline and at the completion of RT. A comparison of the scores obtained with the FACIT-Fatigue subscale and the PROMIS Fatigue-Short Form 8a at baseline and at the completion of RT. A patient survey and chart review will be used to determine the number of hospital admissions, emergency center visits, and medical days off of work.
Study Design:	Double-blind, placebo-controlled trial with participants randomized to melatonin or placebo.
Study Agent/ Intervention Description:	Melatonin (20 mg/day) or placebo, given orally at night, starting on the night before the first day of RT and continuing until 2 weeks beyond the completion of RT.
Number of Patients:	142
Patient Participation Duration:	Approximately 9-16 weeks (1-8 weeks of RT followed by 8 weeks of follow-up)
Estimated Time to Complete Enrollment:	2 years
Statistical Methodology:	A two-sided ANOVA F-test at a 4.5% level of significance for the primary objective will be used if the interim analysis allows the study to continue. Secondary analysis of each of the subscales and ESAS scale will be reported using an F-test at a 5% level of significance after necessary transformation needed for normality of the scores.

SCHEMA


Breast cancer
Randomize to melatonin or placebo
RT (as clinically indicated) + melatonin (20 mg/day, orally at night, starting on the night before the first day of RT and continuing until 2 weeks beyond the completion of RT)
RT (as clinically indicated) + placebo (orally at night, starting on the night before the first day of RT and continuing until 2 weeks beyond the completion of RT)
Evaluation at baseline, every 2 weeks (± 4 days) during melatonin/placebo treatment (for RT durations ≥ 3 weeks), at the completion of RT (± 4 days), 2 weeks post-RT (± 4 days), and 8 weeks post-RT (± 4 days)
Evaluations include: FACIT-F, FACIT-Fatigue, PROMIS Fatigue Short Form 8a, and ESAS scales; correlative sampling for biomarkers

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List of Abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
APBI	Accelerated
AST	Aspartate aminotransferase
CTCAE	Common Terminology Criteria for Adverse Events
CTRL	Clinical and Translational Research Laboratory
DSMC	Data and Safety Monitoring Committee
DSMP	Data and Safety Monitoring Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ESAS	Edmonton Symptom Assessment System
FACIT	Functional Assessment of Chronic Illness Therapy
FDA	Food and Drug Administration
HPA	Hypothalamic-pituitary-adrenal
HRQOL	Health-related quality of life
LSM	Lymphocyte Separation Medium
OHRP	Office for Human Research Protections
PBMC	Peripheral blood mononuclear cells
QOL	Quality of life
RCT	Randomized clinical trials
RT	Radiotherapy
SAE	Serious adverse event
ULN	Upper limit of normal
UP	Unanticipated problem

1 BACKGROUND

1.1 Cancer and Fatigue

Fatigue is the most common symptom in patients with cancer and has a multidimensional construct that includes physical, functional, psychological, and social elements. There are multiple contributing factors to fatigue including pro-inflammatory cytokines, hypothalamic-pituitary-adrenal (HPA) dysfunction, cachexia, and psychosocial factors such as chronic stress and depression. Although supervised exercise improves fatigue in breast cancer patients, home-based interventions did not show the same benefit (1). Currently, there is no effective pharmacological therapy for cancer-related fatigue. Psychoeducational interventions to reduce fatigue during cancer therapy have also not been consistently effective (2).

Fatigue is associated with radiotherapy (RT) for a number of different tumor types (3) and is reported to be present in almost 90% of patients. Patients with early-stage breast cancer receiving RT experience increased fatigue during treatment (4). Radiation-induced fatigue has also been studied in early-stage breast cancer patients receiving one of 3 different radiotherapies (standard whole breast RT [mean of 43 days on treatment]; accelerated partial breast irradiation [APBI; mean of 20.6 days on treatment]; or accelerated hypofractionated RT [mean of 20.8 days on treatment]) (5). In comparison to the fatigue scores obtained at the first treatment visit, fatigue scores for all 3 treatments were only slightly elevated at the midpoint of study treatment visit, were maximally elevated at the last study treatment visit, and were declining but still elevated relative to the midpoint scores. Although fatigue increased for patients on all 3 RT protocols, increased fatigue was more pronounced for the patients undergoing either standard whole breast RT or accelerated hypofractionated RT than it was for patients undergoing APBI. Heightened fatigue prior to treatment and an elevated level of IL-6 soluble receptor during therapy were found to be risk factors for increased fatigue during active radiation therapy (6). An increased pretreatment fatigue level has also been found to be a risk factor for persistent long-term fatigue following treatment completion (7).

A multicenter study has used the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scales in patients receiving radiotherapy for head and neck cancer (8). The detrimental effects on quality of life (QOL) and functional status were significant, and opioid analgesia provided inadequate relief. This study and other reviews (9) suggested preventive rather than symptom palliation measures are needed to improve the QOL in patients receiving radiotherapy. The economic impact could be significant and is a suggested future research goal (10).

RT has been identified as a cause of fatigue in patients with advanced cancer and also in those with localized disease being treated with curative intent. Attenuating the side effects of radiation with concurrent melatonin therapy at the start of RT may prevent exacerbation of fatigue and improve the QOL of cancer patients. Melatonin is an inexpensive, readily available, natural supplement that has been shown to be radioprotective in animal models and safe in humans.

1.2 Melatonin

1.2.1 Preclinical Data

Melatonin given to rats protects against irradiation induced oxidative (11) and chromosomal damage (12), and attenuates acute radiation enteritis (13).

1.2.2 Clinical Data

In humans, multiple studies have shown that melatonin supplementation in patients with cancer has clinical benefits such as decreasing the side effects of radiation and chemotherapy, improving symptoms, and prolonging survival (14). Systematic reviews and meta-analyses of melatonin therapy reported improvement in tumor remission, 1-year survival, and fewer radio- and chemotherapy-related side effects (15-17). Unfortunately, more recent independent randomized controlled trials have not been able to show that melatonin improves survival in patients with brain metastases receiving radiation (18) or improves appetite in patients with advanced GI or lung cancers (19).These recent randomized clinical trials (RCTs) may have failed to show benefit because patients with advanced cancer may be refractory to intervention with melatonin. A strategy of earlier intervention for the prevention of radiation-induced side effects would be more effective at reducing symptom burden and improving the QOL.

1.2.3 Known and Potential Risks and Benefits

Three systematic reviews have examined the benefits and side effects of melatonin as adjuvant therapy for patients with cancer (15-17). Pooled analysis showed benefit on survival (17), with numbers needed to treat ranging between 3 and 5. A subsequent systematic review of 10 randomized controlled trials and meta-analysis also found that melatonin consistently reduced the risk of death at 1 year across all doses and types of solid tumors (15). The meta-analysis concluded that melatonin had few side effects, was innocuous even at high doses, and appeared to have a high safety profile. Although the doses used in the studies were significantly higher (10-50 mg/d) than those used for other indications (0.5-5.0 mg/d), none of the studies found any serious side effects related to melatonin; on the contrary, “melatonin decreased some of the side effects resulting from chemotherapy and radiation therapy.” A meta-analysis (16) of randomized controlled trials (n=761) in patients with solid tumors found no severe adverse events (AEs) and “dramatically decreased radio-chemotherapy related side effects” including neurotoxicity and fatigue.

We conducted a placebo-controlled trial of melatonin in patients with advanced cancer and found that the side effects seen with patients taking 20 mg melatonin were comparable to placebo (no statistically significant difference between the groups) (19). The toxicity of 10 mg of melatonin daily has been evaluated in a randomized double-blind placebo-controlled trial (20). The evaluations included polysomnography and a variety of laboratory tests (eg, complete blood count, urinalysis, sodium, potassium, calcium, total protein, albumin, glucose, lipid profile, blood urea nitrogen, creatinine, liver function tests, thyroid function tests, LH/FSH, and cortisol). In addition, volunteers were asked about possible side effects during the 28-day treatment period. Melatonin did not produce any toxicological alterations,

and the most frequent side effects were headache and somnolence. The placebo group reported a similar frequency of these side effects.

Systematic reviews of melatonin for insomnia (21) or jet-lag lend further support for melatonin's safety, although doses were lower than those used for adjuvant cancer therapy. The systematic review of melatonin for insomnia found no adverse effects, and the review concluded that melatonin was safe for short-term use (< 3 months). The Cochrane database analyzed trials of melatonin (22) for the treatment of jet-lag and concluded that the risks of side effects were low. Somnolence was avoided if melatonin was taken at the correct time before bed.

Review of the Natural Standard's professional monograph of melatonin (23) shows fatigue at doses higher than 50 mg and suggests that caution should be exercised by those operating or driving heavy machinery. Excessive dosages may cause morning sedation or drowsiness. Less severe side effects reported by individuals taking melatonin include: abdominal cramps, confusion, depression, dizziness, anxiety, fatigue, headache, irritability, low blood pressure, nausea, and vomiting. Aspirin, beta blockers, and other NSAIDS may lead to decreased melatonin levels, and the bioavailability of oral melatonin is increased by the co-administration of fluvoxamine (due to the inhibition of the elimination of melatonin). Melatonin and progestin combinations can be additive in inhibiting ovarian function in women, and using melatonin with benzodiazepines, sedating antihistamines, sedating anti-depressants and other sedating drugs may cause additive sedation and increase the incidence of adverse effects. Use of melatonin with corticosteroids may interfere with the efficacy of the corticosteroids and melatonin may decrease prothrombin time (PT). Use of melatonin with alcohol may lead to additive sedation. There are no known interactions with melatonin and food. Use of melatonin with valerian, 5-hydroxytryptophan, or kava may lead to additive sedation. No apparent serious consequences have been reported in those taking up to 24 grams daily of melatonin for one month (23).

Concerns regarding the safety of melatonin or the prospect of diminished efficacy of anti-tumor therapy are not supported by the literature. Our study (19) and others (14) have shown that 20-mg melatonin at night is safe, and further research is justified because "the preponderance of evidence supports a provisional conclusion that dietary antioxidants do not conflict with the use of radiotherapy in the treatment of a wide variety of cancers and may significantly mitigate the adverse effects of that treatment" (24). In addition, there are multiple experimental studies with cancer lines (25) and animal models suggesting that melatonin has an anti-tumor effect (26). Melatonin may also play a role in decreasing incidental cancer since night-shift work has been associated with an increased risk of breast (27) and endometrial cancer (28), possibly as a result of disruption of the circadian rhythm and diminished melatonin production from the pineal gland.

1.2.4 Rationale for Using Melatonin for Fatigue

The mechanisms of fatigue due to RT are multifactorial (29) and include inflammatory processes, a disruption of circadian rhythm, and mitochondrial dysfunction (30). Inflammatory biomarkers such as C-reactive protein are associated with increased fatigue during RT for localized breast and prostate cancer

(31). RT is also associated with decreased muscle endurance which could contribute to an increase in cancer-related fatigue.

There is evidence that melatonin can modulate the mechanisms of RT-induced fatigue. Melatonin decreases the pro-inflammatory immune response, maintains circadian rhythm and sleep quality, and also prevents oxidative damage to mitochondria (32, 33). A meta-analysis of pooled data from 5 trials of patients receiving melatonin during concurrent chemoradiation, found a significantly decreased prevalence of fatigue compared to the control group. Although these trials were randomized, none were placebo-controlled and all were unblinded. Because of these methodological limitations, the efficacy of melatonin needs to be confirmed in a double-blind RCT.

1.3 Project Significance

This would be the first clinical trial using melatonin for prevention of fatigue and other symptoms associated with RT. This inter-programmatic project applies the expertise of Massey Cancer Center collaborators from the areas of Cancer Prevention and Control, Developmental Therapeutics, and Radiation Biology & Oncology.

Recently, a National Cancer Institute Clinical Trials Planning Meeting made recommendations on how to implement high-priority research and clinical trials in cancer-related fatigue, in order to advance the science and reduce symptom burden in this population. Because of the strong likelihood of a placebo effect in cancer-related fatigue, *placebo-controlled trials were recommended* in order to demonstrate efficacy (34). Because of the multidimensional construct of cancer-related fatigue, a future intervention trial may need to be combined with other supportive and behavioral components to produce an optimal result (35), eg, counseling improves the QOL and symptoms in head and neck patients undergoing radiotherapy (36). If our study shows melatonin is effective, future research should consider combination interventions (eg, physical activity, behavioral intervention) for additive or synergistic benefits.

2 OBJECTIVES

2.1 Primary Objective

2.1.1 To determine whether the average increase in fatigue (as measured by the FACIT-Fatigue subscale) from baseline to completion of RT is different in those patients who received melatonin than in those who received placebo.

2.2 Secondary Objectives

2.2.1 To determine whether the average increase in health-related quality of life (HRQOL) from baseline to completion of RT is greater in those patients who received melatonin than in those who received placebo.

2.2.2 To determine whether the average increase in fatigue from baseline until 2 weeks after completion of RT is less in those patients who received melatonin than in those who received placebo.

2.2.3 To determine whether the average increase in fatigue from baseline until 8 weeks after completion of RT is less in those patients who received melatonin than in those who received placebo.

2.2.4 To determine whether the average increase in symptoms from baseline until completion of RT is less in those patients who received melatonin than in those who received placebo.

2.2.5 To determine whether the average increase in fatigue (as measured by the PROMIS Fatigue-Short Form 8a) from baseline to completion of RT is less in those patients who received melatonin than in those who received placebo.

2.2.6 To describe the level of agreement in reported fatigue scores when 2 different survey instruments are used to measure fatigue.

2.2.7 To determine whether patients receiving melatonin have fewer hospital admissions, emergency center visits, and medical days off work than patients receiving placebo.

3 STUDY DESIGN

3.1 General Description

This is a double-blind, placebo-controlled trial wherein patients with breast cancer will be randomized to receive either 20 mg oral melatonin or placebo the night before their first RT, nightly throughout their RT, and for an additional 2 weeks following the completion of their RT. After informed consent is obtained from eligible patients, they will then be electronically randomized on a 1:1 ratio to melatonin treatment or placebo. The patients will be stratified according to treatment duration (less than 3 weeks; equal to or greater than 3 weeks) and prior chemotherapy (yes/no).

3.2 Primary Endpoint

3.2.1 A comparison of FACIT-Fatigue subscale (corresponds to the “Additional Concerns” table of the FACIT-F scale; see Appendix 1) scores obtained at baseline and at the completion of RT.

3.3 Secondary Endpoints

3.3.1 A comparison of FACIT-F (Appendix 1) scores obtained at baseline and at the completion of RT.

3.3.2 A comparison of FACIT-F (Appendix 1) and FACIT-Fatigue subscale (corresponds to the “Additional Concerns” table of the FACIT-F scale; see Appendix 1) scores obtained at baseline until 2 weeks after completion of RT.

3.3.3 A comparison of FACIT-F (Appendix 1) and FACIT-Fatigue subscale (corresponds to the “Additional Concerns” table of the FACIT-F scale; see Appendix 1) scores obtained at baseline until 8 weeks after completion of RT.

3.3.4 A comparison of Edmonton Symptom Assessment System (ESAS) (Appendix 2) scores obtained at baseline until completion of RT.

3.3.5 A comparison of the PROMIS Fatigue-Short Form 8a (Appendix 3) scores obtained at baseline and at the completion of RT.

3.3.6 A comparison of the scores obtained with the FACIT-Fatigue subscale and the PROMIS Fatigue-Short Form 8a at baseline and at the completion of RT.

3.3.7 A patient survey and chart review will be conducted to determine the number of hospital admissions, emergency center visits, and medical days off of work.

[redacted]

4 PATIENT SELECTION

4.1 Inclusion Criteria

A patient must meet all of the following inclusion criteria to be eligible to participate in the study.

4.1.1 Ambulatory outpatients with breast (including ductal carcinoma in situ [DCIS]) cancer

4.1.2 Patients to be treated with RT for curative intent

4.1.3 Women ≥ 18 years of age

4.1.4 ECOG performance status <3 (Appendix 4)

4.1.5 Hemoglobin ≥ 9 g/dL

4.1.6 Either post-menopausal, surgically sterilized, or willing to use an acceptable method of birth control during study treatment and for 3 months afterwards

4.1.7 Patients who are currently taking melatonin must discontinue melatonin for 5 days before enrolling in the study

4.1.8 Ability to understand and the willingness to sign a written informed consent document

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria is ineligible to participate in the study.

4.2.1 Fatigue brought on by conditions other than cancer such as (the indicated tests are required only if that mechanism of fatigue is suspected):

- uncontrolled hypothyroidism (TSH >10 IU)
- hypercalcemia (calcium >11 mg/dL)
  Ca = SerumCa + 0.8 * (NormalAlbumin – PatientAlbumin)
- decompensated congestive heart failure
- chronic obstructive pulmonary disease requiring oxygen replacement

4.2.2 Patients with a creatinine clearance <30 mL/min

4.2.3 Aspartate aminotransferase (AST) > 3 X upper limit of normal (ULN) for the laboratory

4.2.4 Alanine aminotransferase (ALT) > 3 X ULN for the laboratory

4.2.5 Bilirubin > 1 X ULN for the laboratory

4.2.6 Use of systemic steroids, or other pharmacological agents such as methylphenidate for cancer-related fatigue

4.2.7 Current use of American ginseng, remelteon, or warfarin.

4.2.8 Depression ≥ grade 2 (CTCAE v4.0)

5 STUDY ENTRY AND WITHDRAWAL PROCEDURES

5.1 Study Entry Procedures

5.1.1 Competition with Treatment Trials

Priority will be given to treatment trials. A patient will not be approached for participation in this trial until it is determined that either co-enrollment is allowed or that the patient does not want to participate on a treatment trial.

5.1.2 Required Pre-Registration Screening Tests and Procedures

Refer to Section 12, STUDY CALENDAR, for the screening tests and procedures that are required prior to registration, and for the timing of these events relative to the start of treatment.

5.1.3 Registration Process

Patients who meet the eligibility requirements and sign the informed consent form will be registered on the study. Contact the study research nurse, [redacted] for registration:

[redacted]

5.2 Study Withdrawal Procedures

5.2.1 A patient may decide to withdraw from the study at any time.

5.2.2 A patient may be removed from treatment for one of the following criteria:

5.2.2.1 If in the opinion of the treating physician, it is in the best interest of the patient to do so.

5.2.2.2 Sponsor-investigator's decision to discontinue the study.

5.2.3 The reason for withdrawal from the study and the date the patient was removed from the study must be documented in the case report form.

6 TREATMENT PLAN

6.1 Baseline Tests and Procedures

After determination of eligibility, patients will complete a baseline assessment before treatment. Baseline tests are required as indicated in Section 12 (STUDY CALENDAR).

[redacted]

6.3 Additional Treatment Modalities

Patients with localized breast cancer will receive standard-of-care RT as determined by the treating physician. The RT regimens include: (1) 1 week of APBI; (2) 3-4 weeks of an accelerated hypofractionation RT schedule; and (3) 6-8 weeks of a standard RT schedule.

6.4 General Concomitant Medication and Supportive Care Guidelines

No additional concomitant medication or supportive care guidelines are required for this study.

6.5 Duration of Therapy

Patients will receive daily melatonin or placebo beginning the night before their course of RT and for an additional 2-week period that extends beyond the conclusion of their RT.

6.6 Monitoring Patient Compliance

Patients will be given a Study Diary (Appendix 8) to record their use of study medication. The research nurse reviews the diary with the participant and provides assistance with completing the diary if needed.

6.7 Follow-Up Period

Patients will be followed for 8 weeks (± 4 days) after completion of RT or until death, whichever occurs first. Patients removed from the study treatment for unacceptable AEs will be followed until resolution or stabilization of the AE.

7 DOSING DELAYS/DOSE MODIFICATIONS

7.1 Melatonin/Placebo Treatment

7.1.1 A patient with a ≥ grade 3 AE that is possibly, probably, or definitely related to study drug will discontinue treatment with melatonin/placebo.

7.1.2 A patient with a persistent (present over 2 consecutive follow-up intervals) grade 2 AE that is possibly, probably, or definitely related to study drug will discontinue treatment with melatonin/placebo.

7.2 Radiation Therapy

7.2.1 Dosing delays or dose modifications for RT are at the discretion of the treating physician.

8 ADVERSE EVENTS: DEFINITIONS AND REPORTING REQUIREMENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

8.1.2 Suspected Adverse Reaction (SAR)

Any AE for which there is a reasonable possibility that the drug caused the AE. "Reasonable possibility" means that there is evidence to suggest a causal relationship between the drug and the AE.

An AE with an attribution of possible, probable, or definite (see Section 8.1.8 below) is a SAR.

8.1.3 Serious AE (SAE) or Serious SAR (SSAR)

An AE or SAR is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death,
- a life-threatening AE (An AE or SAR is consider "life-threatening" if, in the view of either the investigator or sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or SAR that, had it occurred in a more severe form, might have caused death.),
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or
- a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

8.1.4 Unexpected SAR

A SAR is considered “unexpected” if

- it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed;
- or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.
- “Unexpected” as used in this definition, also refers to SARs that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.5 Unanticipated Problem (UP)

Unanticipated problems include any incident, experience, or outcome that meets all of the following criteria:

- unexpected (in terms of nature, severity, frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.6 AE Description and Grade

The descriptions and grading scales found in the revised Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting.

8.1.7 AE Expectedness

AEs can be ‘Unexpected’ or ‘Expected’.

Expected AEs are listed in Section 8.2 below.

Unexpected AEs are those AEs occurring in one or more subjects participating in the research protocol, the nature, severity, or frequency of which is not consistent with either:

- The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in (a) the protocol-related document, such as

the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or

- The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the AE and the subject's predisposing risk factor profile for the AE.

8.1.8 AE Attribution

- Definite – The AE *is clearly related* to the study treatment.
- Probable – The AE *is likely related* to the study treatment.
- Possible – The AE *may be related* to the study treatment.
- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

8.2 Known AEs List

8.2.1 Melatonin

Likely (10% or more of patients)

- Sleepiness during the daytime
- Headaches

Less Likely (1-9% of patients)

- Abdominal discomfort
- Mild anxiety
- Irritability
- Confusion
- Short-lasting depression
- Dizziness

8.2.2 Breast RT

Likely (10% or more of patients)

- Reddening of the skin during treatment and for several weeks following treatment
- Tanning of the skin lasting months and may be permanent
- Slightly smaller breast size or change in the way the breast looks
- Tiredness and weakness during treatment and for several weeks following treatment
- Swelling of breast
- Peeling of the skin in the area treated with radiation

- Mild pain at the site of radiation treatment requiring over-the-counter pain relievers

Less Likely (3-9% of patients)

- Soreness or tightness in muscles of the chest wall under the treated breast
- Severe pain at the site of radiation requiring prescription pain relievers

Rare But Serious (less than 3% of patients)

- Cough
- Difficulty breathing
- Inflammation of the heart muscle
- Rib fracture
- Slight increase in risk for heart disease for patients with cancer in the left breast
- Risk of developing another cancer

8.3 Time Period and Grade of AE Capture

AEs will be followed from the beginning of study treatment through 30 days following the end of treatment. All AEs, regardless of attribution to study drug, will be captured.

8.4 Procedures for Recording AEs, SAEs, and UPs

Events will be recorded in OnCore.

8.5 Routine Reporting Procedures for AEs

Events will be recorded in OnCore within 30 days of occurrence for those events not requiring expedited reporting.

8.6 Expedited Reporting Procedures for SAEs and UPs

Expedited Reporting Requirements (Events, Report Recipients, and Time Frames)		
SAEs	**UPs**	**SARs**
Sponsor-Investigator[1] Alfredo Urdaneta, MD [redacted]	Sponsor-Investigator[1] Alfredo Urdaneta, MD [redacted].org	FDA[3]
	DSMC[1] [redacted]	
	IRB[2]	

[1] Report event within 2 business days of becoming aware of the occurrence.

[2] Each UP must be reported to the VCU IRB within 5 business days of becoming aware of the occurrence.

[3] The sponsor-investigator will report to the FDA any:

- SARs that are both serious and unexpected within 15 days of determining that the information is reportable.
- clinically important increase in the rate of SSARs within 15 days of determining that the information is reportable.
- unexpected fatal or life-threatening SARs within 7 days of receipt of the information.

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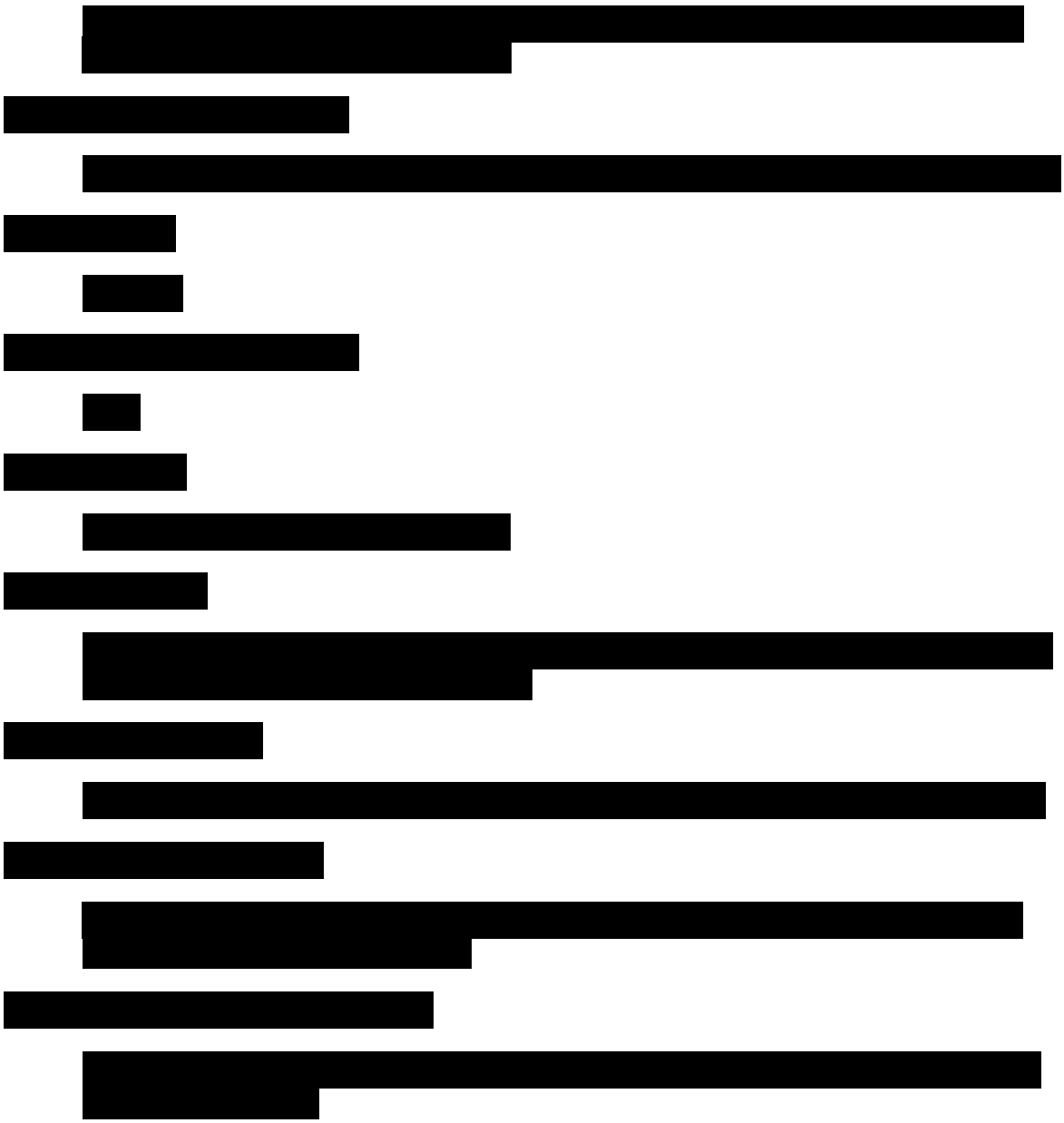


10 MEASUREMENT OF EFFECT

10.1 Fatigue Assessment

Fatigue will be measured using the FACIT-F (Appendix 1) and the FACIT-Fatigue subscale (corresponds to the "Additional Concerns" table of the FACIT-F scale; see Appendix 1) QOL questionnaire (24). The FACIT-F is a well-validated QOL instrument widely used for the assessment of cancer-related fatigue in clinical trials. It consists of 27 general QOL questions divided into 4 domains (physical, social, emotional, and functional), plus a 13-item fatigue sub-score. The patient rates the intensity of fatigue and its related symptoms on a scale of 0–4. The total score ranges between 0 and 52, with higher scores denoting

less fatigue. According to the scoring manual, the negatively worded items on the FACIT-F are reverse-scored so that the higher scores indicate more positive health states (38).

Fatigue will also be measured using the PROMIS Fatigue-Short Form 8a scale (Appendix 3) (34, 39). It consists of 8 general questions regarding fatigue. The patient rates the intensity of fatigue and related symptoms on a scale of 1-5. The total score can range between 8 and 40, with higher scores denoting more fatigue.

Refer to the study calendar (Section 12) for the fatigue assessment schedule.

10.2 Symptom Assessment

Symptoms will be assessed using the ESAS (Appendix 2) (40). The ESAS assesses 10 symptoms experienced by cancer patients during the previous 24 hours: pain, fatigue, nausea, depression, anxiety, drowsiness, dyspnea, anorexia, sleep disturbance, and feelings of well-being (41). The severity of each symptom is rated on a numerical scale of 0–10 (0 = no symptom, 10 = worst possible severity). The ESAS is both valid and reliable in the assessment of the intensity of symptoms in cancer patients (42).

Refer to the study calendar (Section 12) for the symptom assessment schedule.

10.3 Miscellaneous Assessments

10.3.1 ECOG Performance Status

ECOG performance status (Appendix 4) is a simple rating of ability to function in usual activities. It has been widely used by clinicians to evaluate participants in drug clinical trials. It has been adapted (2) for patient self-report.

Refer to the study calendar (Section 12) for the performance status assessment schedule.

10.3.2 Medical History and Physical Exam

Demographics including age, children at home, marital status, ethnicity, income, occupation. Tumor type, histology, and stage. Weight including weight loss within the previous 6 months (per history). Medications including opioids antiemetics, anti-depressants, and anxiolytics. Hospital admissions, emergency center visits, and medical days off from work.

Refer to the study calendar (Section 12) for the assessment schedule.

11 CORRELATIVE STUDIES

11.1 Background

Biomarker Studies: Pro-inflammatory cytokines including IL-1 receptor antagonist (IL-1RA) and IL-6 (31) will be measured to determine if their expression is correlated with fatigue.

Gene Polymorphism Studies: Other investigators have demonstrated that host factors such as cytokine gene polymorphisms may play an important role in the extent and duration of inflammatory processes in breast cancer patients (43) and the associated symptoms of fatigue. These included IL1B -511 C>T (rs16944), IL6 -174 G>C (rs1800795), and TNF -308 G>A (rs1800629) (37). Identifying patients with risk factors for fatigue and could facilitate earlier, more effective therapy.

11.2 Participation in Correlative Studies

Biomarker Studies: Participation in the biomarker studies is a study requirement. Any circumstance that prevents collection, submission or analysis of samples for correlative studies should be reviewed with the sponsor-investigator.

Gene Polymorphism Studies: Participation in the gene polymorphism studies is ***optional***.

11.3 Time Points

11.3.1 Biomarker Studies

The biomarkers will be assessed at baseline, at 2-week (± 4 days) intervals during RT (for treatment durations equal to or greater than 3 weeks), at the completion of RT (± 4 days), at 2 weeks (± 4 days) after completion of RT, and at 8 weeks (± 4 days) after completion of RT.

11.3.2 Gene Polymorphism Studies

Gene polymorphisms in IL1B, IL6, and TNF will be assessed in peripheral blood mononuclear cells (PBMCs) obtained at baseline.

11.4 Sample Labeling

Each sample should be labeled with the following information:

- Study number
- Patient identification number
- “Plasma” (for plasma sample only)
- Total cell number and “PBMC” (for PBMC sample only)
- Date sample was drawn
- Time point (eg, baseline, 2-week, 4-week)

11.5 Procedures, Processing, and Storage

11.5.1 Plasma Samples for Biomarker Studies

Draw peripheral blood into one 6 mL EDTA or sodium heparin collection tube. Gently invert the collection tube 8 times immediately after collection. The sample must be processed within 30 hours of collection. Samples may be held at room temperature if they will be processed within 3 hours of collection; otherwise, the samples should be held in a refrigerator (~2°C to 8°C). If the sample cannot be centrifuged at the site where it is drawn, the sample should be transported to the

MCC Clinical and Translational Research Laboratory (CTRL; see Section 11.6) such that the samples can be processed within 30 hours of collection and such that the proscribed temperatures are maintained (transport on wet or “blue” ice should be used when refrigerated temperatures need to be maintained).

To process, the sample should be centrifuged (1,300 x g, 10 min, 4°C). The plasma should then be separated from the cellular elements by transferring 0.5 mL aliquots of plasma (taking care not to disrupt the cell pellet) into 2 mL polypropylene cryogenic tubes (a sufficient number of tubes should be used to preserve the entire plasma sample).

The plasma samples should be flash frozen in liquid nitrogen (if available) and stored at -20°C for short-term storage (≤ 1 week) and at -70°C to -90°C for long-term storage. The cell pellets should be discarded.

11.5.2 PBMC Samples for Gene Polymorphism Studies

For patients who consent to the optional gene polymorphism studies, draw peripheral blood into one 10 mL EDTA or sodium heparin collection tube. Gently invert the collection tube 8 times immediately after collection. The sample must be processed within 30 hours of collection. Samples may be held at room temperature if they will be processed within 3 hours of collection; otherwise, the samples should be held in a refrigerator (~2°C to 8°C). If the sample cannot be centrifuged at the site where it is drawn, the sample should be transported to the CTRL (see Section 11.6) such that the samples can be processed within 30 hours of collection and such that the proscribed temperatures are maintained (transport on wet or “blue” ice should be used when refrigerated temperatures need to be maintained).

The sample should be processed to isolate PBMCs by using a density gradient separation media such as Ficoll-Hypaque or Lymphocyte Separation Medium (LSM). The processing should be performed by dedicated research personnel according to the manufacturer-specified protocol. The obtained PBMCs should be washed 3 times with phosphate buffered saline and the cell concentration determined. The cell suspension should be centrifuged (250 x g, 10 min at room temperature) in a 1.5 mL microfuge tube, after which the supernatant should be removed without disturbing the cell pellet.

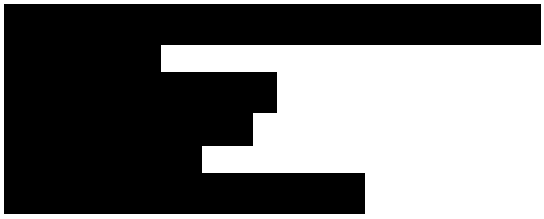
11.5.3 The cell pellet should then be flash frozen with liquid nitrogen and stored at -20°C for short-term storage (≤ 1 week) and at -70°C to -90°C for long-term storage.

11.6 Clinical and Translational Research Laboratory (CTRL)

All samples will be processed by the Massey Cancer Center CTRL, the CTRL should be notified at least 1 day in advance.

CTRL Contact Information (For specimen collection, processing, storage, and transportation questions):

[redacted]



11.7 Sample Analysis

Samples will be stored by the CTRL and evaluated for biomarkers such as C-reactive protein, pro-inflammatory cytokines including IL-1 receptor antagonist, IL-6 (31), plasma citrulline and gene polymorphisms.

12 STUDY CALENDAR

Item	Eligibility[1]	Baseline (Prior to start of RT)	Every 2 weeks (± 4 days) through RT (for RT durations ≥ 3 weeks) and at the completion of RT(± 4 days)[2]	2 weeks (± 4 days) post-RT	8 weeks (± 4 days) post-RT
History & physical exam[3]	x	x	x	x	x
ESAS scale		x	x	x	x
ECOG scale		x	x	x	x
PROMIS scale		x	x	x	x
Hemoglobin	x				
Creatinine	x				
TSH	x[4]				
Ca	x[5]				
CBC	x				
Albumin	x[5]				
Bilirubin, ALT, AST	x				
AE assessment		x	x	x	x
FACIT-F, FACIT-Fatigue		x	x	x	x
Blood collection for biomarker studies (plasma)		x[6]	X[6]	X[6]	X[6]
Optional blood collection for gene polymorphism studies (PBMCs)		x[7]			

[1]Required within 28 days preceding the beginning of therapy.

[2]Patients who have both a 2-week follow-up visit and an end-of-RT visit within a 5-day window will have an end-of-RT visit only.

[3]May be performed by a mid-level provider.

[4]Only required if hypothyroidism is suspected.

[5]Only required if hypercalcemia is suspected.

[6]Draw peripheral blood into one EDTA or sodium heparin collection tube (1 x 6 mL).

[7]For patients who consent to the optional gene polymorphism studies, draw peripheral blood into one EDTA or sodium heparin collection tube (1 x 10 mL).

13 STATISTICAL CONSIDERATIONS

13.1 Study Design and Analysis

This is a double-blind, placebo-controlled trial randomizing participants to 20 mg oral melatonin at night throughout the course of their RT plus an additional 2 weeks. Eligible patients will be electronically randomized on a 1:1 ratio within each stratum to melatonin treatment or placebo. Investigational pharmacists will dispense either melatonin or placebo capsules according to a computer-generated random assignment list. The allocation scheme would keep the allocation ratio approximately equal across all of the strata. Stratification is done according to treatment duration (less than 3 weeks; equal to or greater than 3 weeks) and prior chemotherapy (yes/no).Treatment allocation will be concealed from patients, investigators, and study coordinators enrolling the participants. The statistical collaborator will be unblinded and provide the randomization list to the pharmacy. Interim results needed for Data and Safety Monitoring Committee (DSMC) review will be provided by the research nurse in a blinded manner; however, the statistician can unblind groups to the DSMC if there is a concern. The primary investigators and other collaborators would remain blinded.

The primary hypothesis of no change in fatigue will be tested using the ANOVA F-test after adjusting for duration of RT (binary) and prior chemotherapy. Stratified randomization will be used to keep the groups balanced; however, statistical model will also be adjusting for them. The final hypothesis test level will be adjusted using O'Brien Fleming spending function for type I error. Details of interim analysis are provided in Section 13.6.

13.2 Patient Replacement

Patients (on either the melatonin treatment or placebo arm of the study) who are not evaluable for the primary endpoint because they drop out or are removed from the study prior to completing the FACIT-Fatigue subscale at the completion (± 4 days) of RT will be replaced.

13.3 Sample Size/Accrual Rates

The primary endpoint of the study is the change in FACIT-F score for patients receiving melatonin and the same for patients receiving placebo. In a prior study of a pharmacological intervention for cancer-related fatigue (44), the expected mean and SD of the overall change in FACIT-F score in the placebo group was 13 and SD was 14.78. We assume the same SD for the melatonin subgroup and a clinically meaningful difference is deemed to be a half SD difference which is approximately 7 units. Based on these findings and using a two-sided t-test at 5% level of significance, we would need 71 patients in each of the placebo and melatonin groups for 80% power. Our target cohort size is, therefore, 142 patients.

Compliance is expected to be very high, and the drop-out rate is expected to be minimal. As a result, no adjustment of the sample size is done to accommodate drop outs or lack of compliance; however, the patients dropping out before the completion of the post treatment questionnaire will be replaced.

13.4 Stratification Factors

The patients will be stratified according to duration of radiation treatment (less than 3 weeks; equal to or greater than 3 weeks) and prior chemotherapy (yes/no). Analysis of the primary hypothesis will be adjusted for the stratification factors. However, the sample size computation used only the data available from one strata as there is little knowledge about the effect size in each individual strata. Target power is kept at 80% to protect against possible lack of separation in some strata, keeping the target sample size in a feasible range.

13.5 Analysis of Secondary Endpoints

Secondary analysis of each of the subscales and ESAS scale for each strata will be reported using a 2 sample t-test with necessary adjustment needed for normality of the scores. Cohorts will be tested for homogeneity at baseline with respect to each of the scales. Other secondary outcomes will be summarized in the overall cohort, as well as in each subgroup of patients. Exploratory analysis will be done to identify the patient subgroup with relatively high effect and low effect.

13.6 Interim Analysis

An interim analysis will be performed once one-half of the target patient sample size is accrued and evaluable. The unified family method with rho=0.3 (45) will be used as the spending function to determine the rejection boundary, which is a modified version of the O'Brien Fleming method. As computed by SAS proc Seqdesign, 36 evaluable patients in each arm will be needed to perform this analysis and a standardized absolute z value of 2.49 will be needed to reject the null hypothesis at the interim stage. To maintain a 5% level of significance, the final analysis will be done at the 0.037 level, which is equivalent to using an absolute z score of 2.02 for rejecting the null hypothesis. The sponsor-investigator will remain blinded to the interim analysis, although it will be made available to the DSMC.

14 DATA AND SAFETY MONITORING PLAN (DSMP)

The DSMP for this study will consist of the following 3 elements:

14.1 Study Team

The study team minimally consists of the sponsor-investigator, the research nurse, the clinical research associate, and the study biostatistician. While patients are on treatment, the sponsor-investigator, the research nurse, and the clinical research associate will meet at least monthly, and will meet at least quarterly with the study biostatistician, to review study status This review will include, but not be limited to, reportable AEs and UPs, and an update of the ongoing study summary that describes study progress in terms of the study schema. The appropriateness of further patient enrollment and the specific intervention for

a next patient enrollment are addressed. All meetings including attendance are documented.

14.2 Monitoring and Auditing

14.2.1 MCC Compliance Office

Compliance specialists in the MCC Compliance Office will provide ongoing monitoring and auditing for this trial.

14.2.2 Data and Safety Monitoring Committee

The study will be reviewed by the MCC Data and Safety Monitoring Committee (DSMC) initially according to the risk level specified by the MCC Protocol Review and Monitoring Committee (PRMC) and then according to a schedule based on study status and quality indicators. The DSMC reviews reports of the sponsor-investigator/study team and the MCC Compliance Office focusing on data integrity and patient safety.

15 REGULATORY COMPLIANCE AND ETHICS

15.1 Ethical Standard

This study will be conducted in conformance with the principles set forth in *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, April 18, 1979).

15.2 Regulatory Compliance

This study will be conducted in compliance with:

- The protocol
- Federal regulations, as applicable, including: 21 CFR 50 (Protection of Human Subjects/Informed Consent); 21 CFR 56 (Institutional Review Boards); 21 CFR 312 (IND Application); and 45 CFR 46 Subparts A (Common Rule), B (Pregnant Women, Human Fetuses and Neonates), C (Prisoners), and D (Children)

15.3 Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents and recruitment material by an appropriate IRB registered with the Office for Human Research Protections (OHRP). Any amendments to the protocol or consent materials must also be approved. In the United States and in other countries, only institutions holding a current US Federalwide Assurance issued by OHRP may participate.

15.4 Informed Consent Process

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of this therapy will be provided to the patients and their families. Consent forms describing in detail the study interventions/ products, study procedures, and risks are given to the patient and written documentation of informed consent is required prior to starting intervention/administering study product. Consent forms will be IRB-approved and the patient will be asked to read and review the document. Upon reviewing the document, the investigator or research nurse will explain the research study to the subject and answer any questions that may arise. The subject will sign the informed consent document prior to any procedures being done specifically for the study. The patients should have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The patients may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the subjects for their records. The rights and welfare of the patients will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

15.5 Patient Confidentiality and Access to Source Documents/Data

Patient confidentiality is strictly held in trust by the participating investigators and their staff. This confidentiality includes the clinical information relating to participating patients, as well as any genetic or biological testing.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor-investigator.

The sponsor-investigator will allow access to all source data and documents for the purposes of monitoring, audits, IRB review, and regulatory inspections.

The study monitor or other authorized representatives of the sponsor-investigator may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records.

16 DATA HANDLING AND RECORD KEEPING

16.1 Data Management Responsibilities

The sponsor-investigator is responsible for: (i) the overall conduct of the investigation; (ii) ongoing review of trial data including all safety reports; and (iii) apprising participating sites of any UPs.

The responsible investigator at each site is responsible for: (i) the data management at his or her site; and (ii) reporting SAEs and UPs as required in Section 8.

Any laboratory conducting correlative studies must maintain the laboratory records and documentation (laboratory notebooks, laboratory protocols, print-outs, recordings, photographs, etc.).

16.2 Source Documents

Source documents for clinical information (patient history, diagnosis, clinical and diagnostic test reports, etc.) are maintained in the patient's clinical file. Source documents for the correlative studies are maintained in the laboratory conducting the study.

16.3 Case Report Forms

MCC OnCore data management will provide standard electronic case report forms (eCRFs) and create study-specific eCRFs to capture all the information required by the protocol. The eCRFs will be approved by the study team to ensure the most effective data acquisition. All information on eCRFs will be traceable to the source documents which are generally maintained in the patient's file. All eCRFs should be completed and available for collection within a timely manner, preferably no more than 14 days after the patient's visit.

16.4 Study Record Retention

As applicable, study records will be maintained a minimum of 5 years beyond: (i) the publication of any abstract or manuscript reporting the results of the protocol; (2) the submission of any sponsored research final report; or (iii) submission of a final report to clinicaltrials.gov.

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18 APPENDIX 1. FACIT-F SCALE

The FACIT-F scale is given on the following 3 pages.

FACIT-F (Version 4)

Patient's Initials: _____ Date: _____

Study ID #: _____ Time Point: _____

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

FACIT-F (Version 4)

GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACIT-F (Version 4)

Patient's Initials: _____

Study ID #: _____

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4

GF7	I am content with the quality of my life right now	0	1	2	3	4

FACIT-F (Version 4)

Patient's Initials: _____

Study ID #: _____

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4
An16	I have to limit my social activity because I am tired	0	1	2	3	4

FACIT-F (Version 4)

19 APPENDIX 2. ESAS SCALE

The ESAS scale is provided on the following page. The “Other problem,” listed as the last optional item on the scale, will be sleep. Best sleep=0; worst possible sleep=10.

Patient's Initials: _____

Study ID #: _____

Date: _____

Time Point: _____

Edmonton Symptom Assessment System: Numerical Scale
Regional Palliative Care Program

Please circle the number that best describes:

No pain	0	1	2	3	4	5	6	7	8	9	10	Worst possible pain
Not tired	0	1	2	3	4	5	6	7	8	9	10	Worst possible tiredness
Not nauseated	0	1	2	3	4	5	6	7	8	9	10	Worst possible nausea
Not depressed	0	1	2	3	4	5	6	7	8	9	10	Worst possible depression
Not anxious	0	1	2	3	4	5	6	7	8	9	10	Worst possible anxiety
Not drowsy	0	1	2	3	4	5	6	7	8	9	10	Worst possible drowsiness
Best appetite	0	1	2	3	4	5	6	7	8	9	10	Worst possible appetite
Best feeling of wellbeing	0	1	2	3	4	5	6	7	8	9	10	Worst possible feeling of wellbeing
No shortness of breath	0	1	2	3	4	5	6	7	8	9	10	Worst possible shortness of breath
Best sleep	0	1	2	3	4	5	6	7	8	9	10	Worst possible sleep

Initials _____

Date _____ Time _____

Complete by *(check one)*

- ☐ Patient
- ☐ Caregiver
- ☐ Caregiver assisted

20 APPENDIX 3. PROMIS FATIGUE-SHORT FORM 8A

The PROMIS Fatigue-Short Form 8a is provided on the following page.

Patient's Initials: _____ Date: _____

Study ID #: _____ Time Point: _____

PROMIS Item Bank v1.0 – Fatigue – Short Form 8a

Fatigue – Short Form 8a

Please respond to each question or statement by marking one box per row.

		Not at all	A little bit	Somewhat	Quite a bit	Very much
	During the past 7 days…					
H7 1	I feel fatigued	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3 2	I have trouble starting things because I am tired	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…					
FATEXP41 3	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40 4	How fatigued were you on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP35 5	How much were you bothered by your fatigue on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP40 6	To what degree did your fatigue interfere with your physical functioning?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
FATIMP3 7	How often did you have to push yourself to get things done because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATIMP15 8	How often did you have trouble finishing things because of your fatigue?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

21 APPENDIX 4. ECOG SCALE

ECOG Performance Status Scale (46)	
Grade	**Criteria**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

22 APPENDIX 5. FOLLOW-UP QUESTIONNAIRE

The Follow-Up Questionnaire is given on the following page.

MCC-12-08248: Melatonin supplementation for cancer-related fatigue in patients receiving radiotherapy: A double – blind placebo-controlled trial.

Patient Initials (L,F, M)_____ Patient ID_____ Date_____

Timepoint_____

Follow-up Questionnaire

Weight (assess at all visits): _____ (kg/ lbs)

Height : _____ (cm/in)

BMI: _____

ECOG performance status (assess at all visits): _____

Has the patient had any **hospital admissions** since the last contact? ____
If yes, how many?_____
Reason for Admission: _____
Hospital: _____ Date(s): _____
Hospital: _____ Date(s): _____
(Note: **Obtain a release of information if appropriate**)

Has the patient had any **emergency department (ED) visits** since the last contact? _____
If yes, how many? _____
Reason for ED visit: _____
Hospital: _____ Date(s): _____
Hospital: _____ Date(s): _____
(Note: **Obtain a release of information if appropriate**)

Has the patient had any **medical days off from work** since the last contact?
_____ If yes, how many? _____
Reason for missed days: _____ Date(s): _____
Reason for missed days: _____ Date(s): _____
Reason for missed days: _____ Date(s): _____

Review and Update Medication list :
(please list all opiods, benzodiazepines, prescription sleeping aids, steroids and central nervous system stimulants

_____

_____

_____

_____

_____

_____

Laboratory Studies: Date Obtained: _____

_____ WBC

_____ RBC

_____ Hemoglobin

_____ HCT

_____ PLT

_____ Creatinine (baseline only)

**Note reason if not obtained:_____

Compliance Assessment:

Patient has taken _____ mLs this cycle.
She/he has missed _____ mLs, as indicated on diary.

Comments:

_____
_____
_____
_____

Completed by:_____ Date: _____

23 APPENDIX 6. BLOODWORK FORM

The Bloodwork Form is provided on the following page.

MCC-12-08248: Melatonin supplementation for cancer-related fatigue in patients receiving radiotherapy: A double – blind placebo-controlled trial.

Patient Initials (L,F, M)_____ Patient ID_____
Date_____

Timepoint_____

Bloodwork

_____ WBC

_____ RBC

_____ Hemoglobin

_____ HCT

_____ PLT

_____ Creatinine(baseline only)

24 APPENDIX 7. DEMOGRAPHIC FORM

The Demographic Form is provided on the following page.

Demographic Form

Patient Initials (Last, first, middle):

Gender: _____M _____F _____Unknown

Date of Birth: ____/___/_____ Age:_____

Zip Code: _____

Marital Status:
_____Single, Never Married
_____ Married; Living with significant other
_____ Divorced or Separated

Children:
_____Yes. Ages:
_____
_____No

Date Informed Consent Signed:

_____/ _____/ _____ /

Date HIPPA Form Signed:

_____/ _____/ _____/

Race:
____White
____ Black or African-American
____Native Hawaiian or other Pacific Islander
____ Asian
____ American Indian or Alaska Native
____Not reported (patient refused)
____Unknown (patient unsure)

Ethnicity:
____Not Hispanic or Latino
____Hispanic or Latino
____Not reported (patient refused)
____ Unknown (Patient unsure)

Method of Payment:
____Private Insurance
____Medicare
____Medicare and Private Insurance
____Medicaid
____Military or Veterans Sponsored
____ Self pay (no insurance)
____ Other
____Unknown

Household Income:
____<$20,000
____$20,001 - $40,000
____$40,001 - $60,000
____$60,001 - $80,000
____$80,001 and above

Employment Status:
____Retired
____Unemployed
____Employed (list occupation on next line)
_____

Demographic Form

Medical History

Date of Diagnosis:
_____/_____/ _____/

Pathology:

Stage: T____ N____ M____

Weight prior to cancer diagnosis:

Weight on enrollment into study:

25 APPENDIX 8. STUDY DIARY

The Study Diary is provided on the following page.

BRING THIS DIARY AND STUDY MEDICATION BOTTLE(S) ON EACH CLINIC VISIT, OR AS DIRECTED BY **RESEARCH NURSE.**

Patient's Initials:_____ MR#:_____ Visit:_____ Study Number:_____

Day	**Pre Rad**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**Education of study meds by:** _____ **date:**_____
Date																
Melatonin/ Placebo take 10 ml suspension orally at night	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	___ Missed	**Comments/ Please List Reasons for Missing Study Drug**
SIDE EFFECTS																
Sleepiness during the daytime																
Dizziness																
Headaches																
Abdominal discomfort																
Mild Anxiety																
Irritability																
Confusion																
Short-lasting depression																

Other side effects experienced: _____

_____

_____

Patient has taken _____ml this cycle. She/he has missed _____ml, as indicated on diary.

This diary & suspension dosing log was reviewed with pt by the Research Nurse / CRA _____ DATE _____

26 APPENDIX 9. CONTRACEPTIVE USE AGREEMENT

The Contraceptive Use Agreement is provided on the following page.

MCC-12-08248 Agreement to Use Adequate Contraception

Patient's Initials:

Study Number:

Date:

Because of the effects of radiation and melatonin that are known/unknown to the developing fetus, I am required to agree to use adequate contraception prior to study entry, for the duration of study participation, and 3 months after completion. For the purpose of this study, adequate contraception is defined as any of the following methods: Either post-menopausal, surgically sterilized or willing to use an acceptable method of birth control (all hormone-based contraceptives are deemed to be unacceptable forms of birth control with respect to meeting inclusion criteria). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

I agree to the above and have been given a copy of this document for my records.

☐ The above statement does not apply due to patient's menopausal status.

_____	_____
Patient's Initials	Date
_____	_____
Research Nurse	Date

27 APPENDIX 10. GENERAL INFORMATION ABOUT MELATONIN

A general information sheet to be provided to study patients is shown on the following page.

General Information About Your Study Medication

This bottle contains your study medication, which is melatonin or a placebo.

Please begin taking a 10 mL dose of your study drug at night on _____ and continue taking it every night (including weekends and holidays) while you are receiving radiation treatment and continue to take it for two weeks after your radiation treatment has ended.

Please remember to shake the bottle before you dispense each dose. The 10-mL dose has been marked on the medication cups provided for your use.

Please use the form in the folder that you have been given to record each dose you take or any doses you miss. Also record any side effects that you notice. Your study nurse will be contacting you to check on you the week following your first dose.

If anything changes in your radiation plan, if you stop radiation, or if your radiation treatment is shortened or lengthened, please call your research nurse or ask your radiation nurse to call your research nurse. Unless you are having unacceptable side effects, which is very unlikely, please do not stop taking your melatonin without first speaking with your research nurse.

A brief word about measuring your dose. Your medication cups are marked at the 10 mL point. This is the line we would like you to use when measuring your dose. It is best to place the cup on a flat surface and pour the liquid into the cup. Please be mindful that the best way to view the line is to look at eye level on the side of the cup while the cup is resting on a flat surface.

Thank you for participating in this important clinical trial!

Please feel free to contact your study nurse if you have concerns, questions, or side effects that you wish to discuss.

[redacted]

28 APPENDIX 11. PATIENT RECRUITMENT FLYER

The Patient Recruitment Flyer is provided on the following pages.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

VCU MASSEY CANCER CENTER

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]