

Research Article

MELADERM-trial: Melatonin cream against acute radiation dermatitis in patients with early breast cancer: a phase-2, double-blind, randomized, placebo-controlled trial: a protocol article

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ABSTRACT

Radiation dermatitis following radiation therapy in the treatment of early breast cancer can lead to discontinuation or prolongation of treatment and an impaired quality of life. Melatonin has been demonstrated to protect against radiation injury. The aim of this study is to investigate whether melatonin can protect against radiation dermatitis when applied topically in women receiving radiation therapy for early breast cancer. This study will be a randomized, placebo-controlled, double-blind controlled trial. Patients will apply the melatonin or placebo preparation topically twice daily for the duration of their radiation therapy. Our objective outcomes will be the Radiation Therapy Oncology Group's acute radiation morbidity scoring criteria for skin, image analysis of clinical photographs, and use of steroid cream for radiation dermatitis. Subjective outcomes will be quality of life questionnaires developed by the European Organisation for Research and Treatment of Cancer. Outcomes will be measured throughout the five weeks of radiation treatment and be followed up for another three weeks. According to sample-size calculations and inclusion schedule, we intend to include a total of 80 evaluable patients. We will analyze the primary outcomes using parametric and non-parametric tests where applicable. Secondary outcomes will be analyzed by a mixed linear model. Most patients with breast cancer who undergo radiation therapy will develop radiation dermatitis as a result of the therapy. Should our intervention provide better outcomes, many patients could obtain a better quality of life. We expect topical melatonin treatment to have little or no adverse effects, to be easy to apply, and not to interfere with the anti-tumor efficacy of the radiation therapy.

Keywords: radiation dermatitis, radiotherapy, breast cancer, melatonin, randomized controlled trial, protocol, RTOG, EORTC, quality of life

Trial registration: The current trial was registered at clinicaltrials.gov (Registration ID: NCT03716583) on October 23, 2018 (<https://clinicaltrials.gov/ct2/show/NCT03716583>) Furthermore, the trial is registered in the European Clinical Trials Database with EudraCT number: 2018-001705-91.

1. INTRODUCTION

Radiation injury is a common serious adverse reaction to treatment of various cancers with ionizing radiation [1-8]. In treatment of breast cancer, the most common complication of radiation therapy is radiation dermatitis [9]. During the course of radiation therapy, most patients (74-100%) will experience radiation dermatitis [10]. Symptoms of acute radiation dermatitis include pruritus, discomfort, and local pain [11], with a negative impact on the patients' quality of life [12]. Radiation dermatitis can even limit the therapeutic dose of radiation delivered to the patient, and lead to interruptions or prolongation of treatment [9].

The hormone melatonin reduces oxidative stress [13, 14]. A previous study, demonstrated the radioprotective effect of melatonin in the treatment of breast cancer [11]. This study included patients receiving breast-conserving surgery and randomized them to receive either melatonin or placebo in a cream, which was applied twice daily. This study demonstrated a protective effect of melatonin against radiation dermatitis in women receiving a total dose of 50 Gy (2 Gy per fraction) [11]. However, they did not state the dose of melatonin applied and only used the RTOG scale as an outcome. No subjective outcomes were measured [11]. The authors have not been able to inform us of the dose of melatonin used.

The aim of the present randomized double-blind placebo-controlled clinical trial is to investigate whether melatonin can protect against acute radiation dermatitis in patients with early breast cancer receiving radiation therapy, and if this has an impact on the patients' quality of life

2. METHODS

The study is a randomized, placebo-controlled, double-blind clinical trial. Patients will be allocated in a ratio of 1:1 to the melatonin/ dimethyl sulfoxide (DMSO) or placebo cream group. Patients will be stratified according to the type of surgery (lumpectomy or mastectomy). Randomization will be performed in blocks of randomized sizes. Our study will be performed at the Department of Oncology at Rigshospitalet, Denmark. Patients will be included into our study according to our eligibility criteria (see Table 1). This study is registered at clinicaltrials.gov (Registration ID: NCT03716583) as well as in the European Clinical Trials Database (EudraCT) (Registration: 2018-001705-91).

2.1. Table 1: Inclusion and exclusion criteria.

Inclusion criteria
Diagnosed with early breast cancer
Over 49 years old
Have had radical surgery (lumpectomy or mastectomy)
Follows treatment regimens and follow-up at Rigshospitalet
Written informed consent after written and verbal information
Exclusion criteria
Inability to understand Danish, written or spoken
Mental illness*
Previous therapy with ionizing radiation in the thoracic or neck area
Use of bolus for radiation therapy**
Pregnancy***

* Defined as having a diagnosis and being in medical treatment, or if anticipated poor compliance. ** A bolus is

*a material which has dose absorption properties equivalent to tissue. It is placed on the irradiated area to alter dosing or target of the radiation therapy. *** Patients will be asked to take a pregnancy test prior to inclusion*

2.2. Interventions.

Patients with early breast cancer treated with lumpectomy all undergo adjuvant radiation therapy over 15 to 30 fractions of ionizing radiation to a total of 40-60 Gy within 3-5 weeks according to the guidelines of the Danish Breast Cancer Cooperative Group [15]. In our study, the patients will apply approximately 1 g of cream containing melatonin/DMSO (25/150 mg/g) or a placebo cream topically twice daily on the area in which they receive radiation therapy. We have chosen to dissolve melatonin in DMSO due to the poor solubility and stability of melatonin in watery solutions. DMSO has previously been used as a stabilizer and penetration enhancer in other topical solutions [16]. DMSO makes it possible to store the cream at room temperature for extended periods with no degradation of melatonin. We have chosen placebo as our comparator due to its being safe, and in our view the most reasonable method of evaluating any effects of the intervention. Participants will apply the cream twice daily from the first to the last fraction of radiation therapy. On days when the patients receive radiation fractions, the melatonin/DMSO or placebo cream will be applied no less than 2 hours prior to radiation.

Throughout the study, the patients will meet with an investigator once weekly who will monitor compliance. In patients requiring steroid cream as a treatment for their radiation dermatitis, the use of this will be monitored. The patients will be recommended not to apply any other topical treatments to the irradiated area during the study. The use of other local therapeutics will be registered.

2.3. Primary outcomes.

The Radiation Therapy Oncology Group's (RTOG) acute radiation morbidity scoring criteria for skin will be used as the primary outcome of the study [17]. The RTOG scale is widely used as a measure for radiation injury in the skin [17, 18].

Furthermore, an evaluation of the erythema will be performed with image analysis of clinical photographs after radiation exposure. Erythema has previously been evaluated by a validated method using software analysis (Image J, version 1.45S, National Institute of health, USA) of digital photos [19]. A "color space converter" function will be used to convert the clinical photos into red/white color scale in the software analysis. Erythema will be quantified by pixel color analyses where all white-colored pixels represent erythema. An a^* -value will represent degree of erythema. A high a^* -value represents a high degree of erythema. This method has previously been used in a study evaluating erythema developed as a result of ultraviolet radiation [20]. Photographs will be taken with the same camera in the same lighting conditions for each picture.

The QLQ-BR23 questionnaire, which evaluates the quality of life in breast cancer patients, was developed by the European Organisation for Research and Treatment of Cancer (EORTC). It is a broadly used and been validated in Danish [21, 22]. The questionnaire includes several items of interest, but specifically for this study, we will focus at breast symptoms as a primary outcome. The remaining items from the questionnaire will be considered secondary outcomes, as described below.

2.4. Secondary outcomes.

The QLQ-C30 is a questionnaire concerning the quality of life in cancer patients in general, which is widely used and has been validated in Danish [23]. All items in the QLQ-C30 as well as the items from QLQ-BR23 (cf. above) that are not mentioned under primary outcomes will be considered secondary

outcomes. Demographic and background variables will be collected at baseline (see Table 2 for a full list of demographic and background variables).

2.5. Table 2: Demographics and background variables.

Demographics	Source
Age	CPR-number ¹
Weight	Patient
Height	Patient
Ethnicity	Patient
Bra size	Patient
Breast volume	Radiation treatment plan
Skin-type ²	Investigator evaluation
Comorbidities	Patient/electronic health record
Connective tissue diseases	Patient
Disease and treatment	Source
Tumor type	Pathology report
Tumor size	Surgical report
Location of tumor	Surgical report
Lymph node status	Pathology report
Metastases	Electronic health record
Axillary dissection	Surgical report
Chemotherapy prior to radiation	Electronic health record
Type of chemotherapy	Electronic health record
Radiation dosage	Radiation treatment plan
Hypo-/hyperfractionation of radiation therapy	Radiation treatment plan

¹Central Person Register in Denmark. ²Fitzpatrick scale.

2.6. Data management.

All outcomes will be collected at the time points noted in Table 3. All data entered into the electronic case report form (CRF), will be data-validated through “required fields” and format (e.g. date-format) where applicable. All outcomes not directly entered (e.g. image analyses) will be imported into the electronic case report form. The data will be stored electronically in Research Electronic Data Capture (REDCap), an electronic research database used throughout the Capital Region of Denmark. All confidential data will be stored in a secure server for 15 years after patient enrollment in the study. Only the investigators and the Good Clinical Practice (GCP) Unit will have access to these data. After conclusion of the study, a final anonymized dataset will be available to RepoCeuticals ApS, the company that has provided a research grant to cover study expenses. Ownership of data is shared between the investigators and RepoCeuticals ApS.

2.7. Participant timeline.

The participant timeline is outlined in Table 3. At the pre-screen consent, the patients will be informed that they have a right to 24 hours of consideration prior to deciding to participate in the trial or not. Oral and written consent will be obtained by an investigator at the time noted in Table 3, or at a maximum 24 hours hereafter. There will be no post-trial care for the participants, other than following the treatment regime offered at Rigshospitalet.

2.8. Table 3: Participant timeline.

Activity/assessment	Pre-study screening/ consent	Pre-study baseline/ randomization	First radiation fraction	Study visit week 1	Study visit week 2	Study visit week 3	Study visit week 4	Study visit week 5	Last radiation fraction	Follow-up week 1	Follow-up week 2	Follow-up week 3
Prescreening consent	●											
Screening log	●											
Consent form	●											
Inclusion/exclusion form	●											
Randomization/allocation		●										
Demographics questionnaire		●										
Instruction in application of cream		●										
Twice daily application of cream			←—————→									
Evaluation of compliance			●	●	●	●	●	●	●			
RTOG score evaluation ^a			●	●	●	●	●	●	●	●	●	●
Clinical photograph			●	●	●	●	●	●	●	●	●	●
QLQ-C30 ^b			●	●	●	●	●	●	●	●	●	●
QLQ-BR23 ^b			●	●	●	●	●	●	●	●	●	●
Steroid usage evaluation			●	●	●	●	●	●	●	●	●	●
Monitoring of adverse events			●	●	●	●	●	●	●	●	●	●
Conclusion of participation												●

^a RTOG score = Radiation Therapy Oncology Group cooperative group common toxicity criteria. ^b QLQ-C30 and QLQ-BR23 = European Organisation for Research and Treatment of Cancer quality of life questionnaires. ^d Serious Adverse event form will be filled in as needed throughout the trial.

2.9. Randomization and blinding.

Patients will be randomly assigned to either a control or experimental group allocated in the ratio of 1:1 by use of a computer-generated randomization schedule. Patients will be stratified according to whether they have undergone lumpectomy or mastectomy. We will randomize the block size to between 4 and 8 patients per block. Block size will be concealed to the investigators until the end of the trial. The allocation sequence will be generated by a staff member with no other involvement in the trial. Assignments will be placed in sequentially numbered, opaque, sealed envelopes with the randomization number printed on them. These envelopes will be packed by a staff member with no other involvement in the trial. Every assignment will contain a code that corresponds to tubes of the melatonin/DMSO or placebo cream. An investigator will enroll and assign participants to intervention on the basis of the assignment code from the envelope. Outcome assessment will be performed by the investigators, who are blinded to treatment allocation.

Participants are also blinded to treatment allocation. The primary investigator will be blinded when performing data analysis and statistical evaluations.

In case of a sudden unexpected serious adverse reaction (SUSAR), the primary investigator will evaluate whether there is a need for the patient's treatment allocation to be unblinded. Treatment allocation will only be unblinded if it is imperative to the treatment of the SUSAR. The treatment allocation will in this case only be revealed to one other investigator than the primary investigator. This investigator will oversee the treatment of the SUSAR.

2.10. Dropouts.

We plan to promote participant retention and complete follow up by asking for contact information (phone number and e-mail) and preferred way of contact. We will schedule appointments with patients at the same location, accommodating their calendar as far as possible.

If a patient does not wish to complete all three follow-up visits, some of the outcomes can be filled in electronically from home, should the patients wish to do so. These outcomes are the QLQ-C30 and QLQ-BR23 questionnaires, and steroid usage outcomes. All data from dropouts will be used in statistical analyses. Discontinuation of treatment will only occur in the following eventualities: if the patient withdraws consent, or if the sponsor decides to terminate the study due to serious adverse events.

2.11. Sample size calculations.

To establish the number of patients needed for the study, we performed 3 separate sample-size calculations. The sample size calculation for the RTOG acute radiation morbidity scoring criteria are based on the findings in a previous study examining melatonin cream as a radio-protector of the skin in patients receiving radiation therapy for breast cancer [11]. In this study, at two weeks' follow-up, 41% of the patients receiving melatonin had toxicity grade 1-2 vs 90% of the patients receiving placebo.

Incidence in placebo group: 90%

Incidence in melatonin group: 41%

Alpha: 5%

Beta: 20%

Sample size needed: Two groups of 14 patients, totaling 28 patients.

The sample size calculation for the image analysis is based on the study evaluating erythema after exposure to ultraviolet radiation [19]. Data for the sample size calculation were obtained from the authors. We assume that the erythema based on ultraviolet radiation can be a reasonable substitute for acute radiation dermatitis, based on erythema being a part of the RTOG acute radiation morbidity scoring criteria grade 1 and 2 [17]. Based on the study used for the RTOG sample size calculation, we assume that the erythema will be most pronounced 2 weeks after conclusion of radiation therapy. We also assume that melatonin applied twice daily in a 2.5% cream, will provide a dose comparable to the 12.5% used in the study evaluating ultraviolet radiation [18], due to a deposition effect in the skin [24]. Furthermore, we have been informed by the authors of the previous study utilizing the 12.5% cream that the cream was not homogenous, and there were small granules of undissolved melatonin in the 2.5%, 5%, and 12.5% creams used. This suggests that the dose required to obtain an effect was in fact smaller than 12.5%. The sample size is calculated based on the a^* -values, where a high a^* -value corresponds to a higher degree of erythema.

Mean (SD) a^* -value for placebo at all time points: 18.4 (3.47)

Mean (SD) a^* -value for 12.5% melatonin cream at all time points: 13.44 (2.36)

Alpha: 5%

Beta: 20%

Sample size needed: Two groups of 8 patients, totaling 16 patients.

The sample size calculation for the QLQ-BR23 breast symptom score is based on a study investigating quality of life following radiation therapy, comparing mastectomy to breast conservation therapy, in breast cancer patients [25]. The data used for the sample size calculation are based on the patients receiving breast-conserving therapy, on their last day of radiation. The 142 patients scored a breast symptom score mean (SD) of 82.2 (15.1).

Mean (SD) α -value for breast symptoms: 82.2 (15.1)

We aim to reduce the breast symptom score to 70.

Alpha: 5%

Beta: 20%

Sample size needed: Two groups of 24, totaling 48 patients.

Because we have three sample size calculations, resulting in required sample sizes of 28, 16, and 48 patients, respectively, and when considering the risk of dropouts, we estimate to include a total of approximately 80 patients. This is based on the inclusion schedule, where the required 48 patients finalizing all data for the outcome parameters have to be completed, will require an inclusion larger than 48 patients. This is because there will be 8 weeks from inclusion to obtaining the data point at two weeks after ended radiation therapy. Thus, we will include continuously in randomized blocks until patient 48 has completed the 8 weeks data point. If we get less than 24 patients in one group completing the 8-weeks data point, additional blocks will be included, until we have at least 24 patients in each group. The staff-member responsible for the randomization sequence will inform the investigators how many patients they will need to include to reach this point because of the randomization of the block size. During 2016, Rigshospitalet treated 194 patients who matched our inclusion criteria. Therefore, we find it feasible to finish inclusion in approximately 6-12 months.

2.12. Statistical analyses.

Normality of data will be assessed through visual inspection of histograms and Q-Q plots. Normally distributed data will be analyzed with parametric tests (e.g. unpaired t-tests), and non-normally distributed data will be analyzed with non-parametric tests (e.g. Mann-Whitney U test). Our primary outcomes are the RTOG scores and the image analysis two weeks after the last radiation fraction, as well as the QLQ-BR3 breast symptoms on the last day of radiation therapy. Our secondary outcomes will be analyzed as follows: We will analyze steroid usage using two different outcomes. Days of steroid usage will be analyzed by either parametric or non-parametric tests. Any steroid usage (yes/no) will be analyzed through χ^2 or Fisher's Exact test. The RTOG scores, the quality of life questionnaires, and the image analysis values for the entire period will be analyzed in a mixed linear model, which takes correlation between patients into account. Subgroup analyses will be performed for mastectomized and lumpectomized patients respectively, if feasible. Other subgroup analyses may be performed based on background variables (fractionation schedule, histopathology and demographic data). Missing data will be taken into consideration when using the mixed linear model. A detailed statistical analysis plan will be formulated and be supervised by a bio-statistician prior to study start.

2.13. Monitoring.

This study will be conducted in compliance with the protocol, EU ICH-GCP guidelines and the applicable regulatory requirements. The standard procedures for quality control and quality assurance are followed in compliance with the ICH-GCP guideline, and investigator/sponsor allows direct access to data/documents for monitoring, auditing, and inspection from both Danish Medicines Agency and the Good Clinical Practice (GCP)-unit. The study will be audited by the GCP Unit of the University of Copenhagen. The GCP Unit will be independent from the investigators and sponsors and have direct access to the electronic case report forms as well as the trial master file. The GCP Unit will also perform data monitoring. The GCP Unit is an independent unit that manages clinical trials in Denmark. No interim analyses have been planned. Currently, a monitoring schedule has not been formulated.

2.14. Harms.

The subjects will be questioned about adverse effects once weekly during treatment. An adverse effect is defined as any medical effect that leads to an unwanted effect in the subject after the administration of the intervention medication, without any necessary connection between the adverse effect and the radiation treatment. An adverse reaction is defined as harm or unwanted reaction to a drug, no matter the dosage. We have defined seven pre-specified self-reported symptoms (nervousness, confusion, depressed mood, dizziness, headache, burning sensation on the skin, and garlic taste or odor), based on the most commonly reported adverse reactions of melatonin and DMSO available in the literature [15, 26-31]. We expect minimal adverse reactions from DMSO, as the degree of toxicity of DMSO is closely related to the dose of DMSO. Lower doses give less toxicity. Further, when applied topically the side effects caused by DMSO are transient and mild, often lasting only minutes [31]. Patients will also be asked to report additional symptoms of adverse effects, if any.

Serious adverse events (SAE) are defined as any medical effect that result in death, are life-threatening, lead to hospitalization, result in disability or permanent damage, or any other important medical event. All serious adverse events will be registered and reported to the Danish Medicines Agency (Lægemiddelstyrelsen) and the local ethics committee (Videnskabsetisk Komité) in a final report.

Serious adverse drug reactions (SARs) will be reported annually. Most likely this will not be applicable to this study, as it will take under a year. In this case, SARs will be reported on conclusion of the study.

Sudden unexpected serious adverse reactions (SUSARs) will be reported immediately to the Danish Medicines Agency and local ethics committee. Adverse event registration will commence on the first study day and be finalized after the last study day. In case of serious adverse reactions, the sponsor can decide if the study will be terminated.

2.15. Approvals.

The study will be performed in accordance with the Helsinki II declaration. Approval from Danish Data Protection Agency (Datatilsynet) has been granted (RH-2018-28, I-Suite no. 6182) in accordance with The Act on Processing of Personal Data (Persondataloven). The study has been approved by the local ethics committee (reference number: H-18037277) as well as the Danish Medicines Agency (Lægemiddelstyrelsen) (EudraCT-no. 2018-001705-91).

2.16. Protocol amendments.

Currently there are no protocol amendments (October 2018). Should any protocol amendments arise, these will be communicated to the investigators, Trials, clinicaltrials.gov, the Good Clinical Practice Unit, the Danish Data Protection Agency, the local ethics committee, and the Danish Medicines Agency.

2.17. Dissemination policy.

Two publications will be written on the basis of this study:

- An article concerning the acute radiation dermatitis measured with the RTOG scale, image analysis and the need for steroid treatment;
- An article concerning the impact of acute radiation dermatitis on the patients' quality of life.

The two articles will be published in international peer-reviewed scientific journals. Both negative, positive, and inconclusive results will be published. The determination and documentation of authorship will be based on the authorship criteria formulated by the International Committee of Medical Journal Editors (ICMJE). Participants will be offered a copy of the articles when published.

3. DISCUSSION

This protocol describes a randomized, placebo-controlled, double-blind clinical trial, comparing melatonin/DMSO versus placebo as protection against radiation dermatitis in early breast cancer. This study will assess both objective (RTOG scale, image analysis, and steroid usage) and subjective outcomes (quality of life questionnaires).

Our study aims to reduce the prevalence and severity of radiation dermatitis in patients undergoing radiation therapy for breast cancer, through the application of topical melatonin and DMSO. Melatonin has been demonstrated to possess antineoplastic and pro-apoptotic effects in cancers in experimental studies [32, 33]. Furthermore, melatonin has been demonstrated to sensitize human breast cancer cells to ionizing radiation in cell culture studies, leading to increased apoptosis in the cancer cells [34, 35]. Thus, melatonin may potentially also have a beneficial effect on the patients' malignant disease although our study is not powered to elucidate this issue.

If the intervention provides better outcomes for our patients, a large number of future patients could potentially receive the treatment, and thereby obtain a better quality of life, and possibly also a reduced need for treatment with glucocorticoid cream. The advantages of the proposed treatment are that it is expected to have little or no adverse effects, to be easy for the patients to apply, and not to interfere with the current treatment regimens

Trial status.

This is protocol version 1.0, 13/09/2018. Patients are not currently being recruited or enrolled. The anticipated start date of enrolment of patients is in December 2018.

List of abbreviations.

CRF: Case Report Form

DMSO: Dimethyl sulfoxide

EORTC: European Organisation for Research and Treatment of Cancer

EU: European Union

EudraCT: European Clinical Trials Database

GCP: Good Clinical Practice

ICH-GCP: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use: Good Clinical Practice

QLQ-BR23: Quality of Life Questionnaire – Breast Cancer Module

QLQ-C30: Quality of Life Questionnaire - Core Questionnaire

REDCap: Research Electronic Data Capture

RTOG: Radiation Therapy Oncology Group

SAE: Serious Adverse Event

SAR: Serious Adverse Drug Reactions

SUSAR: Sudden Unexpected Serious Adverse Reactions

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AUTHORSHIP

All authors made substantial contributions to the design of the study. DZ and JR drafted the manuscript, and it was critically reviewed by CK and FM. All authors read and approved the final manuscript.

DECLARATIONS

A. Ethics approval and consent.

Ethical approval was obtained from the Ethics Committee of the Capital Region of Denmark (reference number: H-18037277). Informed consent is obtained for all patients.

B. Consent for publication.

Not applicable.

C. Availability of data and materials.

Request for access to trial data will be considered, and approved in writing where appropriate, after formal application to DZ and JR.

D. Conflict interests.

None of the authors has any conflicts of interests to declare.

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