Topical cream containing nanoparticles with vitamin E to prevent radiodermatitis in women with breast cancer: a clinical trial protocol

Objective: Little is known about the efficacy of products aiming to prevent radiodermatitis, which affects between 90–95% of women with breast cancer. The use of antioxidants is promising, however, there is a lack of evidenceon their effectiveness. Here, the authors present a clinical trial protocol to evaluate the effects of applying a cream containing nanoparticles with vitamin E to prevent radiodermatitis in patients with breast cancer.

Method: The protocol recommends that 108 women with breast cancer,receiving radiotherapy, are included in this triple-blinded, randomized, controlled study at an oncology hospital. Patients will be divided in three groups of 36 individuals each: group A will receive a cream with lipid nanoparticles and vitamin E, group B will receive a cream without nanoparticles nor vitamin E, and group C will receive a cream with nanoparticles without vitamin E. The primary endpoints will evaluate the incidence, degree, and time of onset of radiodermatitis. The secondary endpoints will focus on the quality of life, symptoms, and local temperature. Patients will be assessed three times a week, from the start of their radiotherapy treatment to two weeks after the last session. This protocol was approved by the research ethics committee of the institutions involved and registered on an international trials database.

Conflict of interest: None.

radiodermatitis • breast cancer • nanoparticles • vitamin E • protocol

Breast cancer is the second leading cause of death in the world female population.[1] In Brazil, the risk of development is 56.3 cases per 100.000 women.[2] One of the treatment modalities is radiation therapy, and up to 60% of cancer patients will undergo this treatment at some point.[3–5]

Radiation therapy is characterized by the use of ionizing radiation to affect the environment in which it is applied. It acts on the cell's DNA, preventing it from reproduction and inducing its death through apoptosis.[6–8] In the case of breast cancer, radiation therapy is used as an adjuvant treatment following a radical mastectomy to decrease the local recurrence rates, and to improve the overall survival (this is, the disease-free time that patients will have after treatment).[9]

Approximately 90–95% of patients treated with external radiation therapy (teletherapy) develop some degree of radiodermatitis.[3,10] This cutaneous reaction is characterized by acute inflammation, moist and dry desquamation, which cause the loss of the epidermis and, in severe cases, the dermis.[5]

Due to its rapid cell renewal, the skin is considered a radiosensitive organ.[11] When skin cells are stimulated by ionizing radiation, water molecules inside them are destroyed through a process called hydrolysis, producing reactive oxygen species (ROS) which cause tissue oxidative stress. This destroys the membranes and the DNA of subjacent cells, leading to acute inflammation.[5]

These injuries affect women's quality of life as they can experience local tenderness, pain, burning and itching, which complicates the process of dressing and caring for oneself, and can contribute to the increased cost of global cancer treatments.[11,12] Women with radiodermatitis have a higher risk of abandoning the radiation therapy or having it suspended by medical indication, compromising the

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localized control of the tumor.[3,11,13]

Despite the research carried out for the prevention of these injuries, relatively few studies in the literature, and the clinical practice, are usually based on local traditions or expert opinions.[5,9,14–17] The use of a topical moisturizer with the indicated skincare practices of the irradiated area, is recommended.[4,17] According to a systematic literature review, products such as topical corticosteroids fail to demonstrate their effectiveness in radiodermatitis prevention prospectively.[5,9,18] Therefore, more evidence needs to be generated to confirm or refute these recommendations.

In correspondence with the pathophysiology of radiodermatitis injuries and the existent oxidative stress, antioxidant treatments are promising for their prevention.

Theoretically, they could complement the local molecular defense mechanisms and counteract oxidative stress effects.[19–25] Among them, vitamin E is highlighted in the literature, which acts as a cofactor for an enzymatic antioxidant molecular complex protecting cells against damage.[22,26]

Nanotechnology can be used to carry active components through the skin to increase penetration, concentration, bioavailability, and efficacy.[18,27–33] However, few clinical studies have explored vitamin E encapsulation in nanoparticles to prevent radiodermatitis, thus demonstrating the need for new scientific evidence.[16]

Objective

The general objective of the clinical trial is to evaluate the potential effect of the application of a cream containing lipid nanoparticles with vitamin E (2%) to prevent acute radiodermatitis in women with breast cancer who underwent radiotherapy. The authors will consider the following hypothesis: patients undergoing radiotherapy, and who are following standard care to prevent radiodermatitis and applying a topical cream containing lipid nanoparticles with vitamin E with a final concentration of 2%, will present a lower incidence and degree of radiodermatitis, and/or a delay in the onset of skin reaction to ionizing radiation in comparison to patients who, in addition to following standard care, are applying a cream with empty lipid nanoparticles (without vitamin E), or cream without lipid nanoparticles nor vitamin E.

Specifically, the authors aim to identify and compare the incidences and degrees of radiodermatitis severity in the three different treatment groups in the total sample and stratified by the number of radiotherapy sessions; to evaluate and compare the time of onset of skin reactions by degrees; to identify the frequency and location of the radiodermatitis specific features; to study the health-related quality of life perceived by patients at the beginning and at the end of radiotherapy; to evaluate and compare the local symptoms reported by patients during radiotherapy treatment; and finally to verify the temperature of the irradiated breasts in comparison to the contralateral breasts during radiotherapy in the three study groups.

Method

Study design

The authors will develop a randomized, controlled, parallel, prospective, triple-blind clinical trial regarding prevention registered in the Brazilian Registry of Clinical Trials (REBEC), No. RBR-784F3Y; Universal Trial Number (UTN) U1111-1201-5923. It will follow the international guidelines and recommendations of the Consolidated Standards of Reporting Trials (CONSORT) for this type of study.[34–36]

Patients will be distributed into three groups:

- Group A (intervention): this group will topically apply a cream containing nanoparticles with vitamin E (concentration of 2%).
- Group B (control 1): this group will topically apply a cream containing nanoparticles without vitamin E.
- Group C (control 2): this group will topically apply a cream, without nanoparticles nor vitamin E.

The composition and function of the base of the cream that will be used in the three groups are described in Table 1. It consists of a cream with a basic formulation which will only hydrate the skin, and will serve as a standard intervention for all groups.

The active ingredient, the nanoparticles with

vitamin E, is manufactured in Brazil and will be purchased commercially according to accessibility (Croda®, Brazil). The safety and quality will be verified by the manufacturing company which will have to be registered in the Brazilian national health surveillance system. This raw material will be added to the base cream in a regular compounding pharmacy authorized for this purpose.

The nanoparticles selected for this study are nanostructured lipid carriers arranged in a homogeneous, white and opaque liquid of colloidal suspension. They are composed of a mixture of solid and liquid lipids with different carbon chains and an aqueous base with one or more surfactants which constitutes a heterogeneous matrix that allows a greater capacity for the incorporation of active ingredients.[37,38] This approach is currently recognized as a new generation of drug delivery systems.[39]

In addition to the characterization and clinical safety test results provided by the manufacturer of the nanoparticles (Croda®, Brazil), the researchers performed laboratory analysis for the nanoparticle characterization (size stability, dispersion and rheological behaviour) to obtain better knowledge regarding the product. Also, skin penetrability and transepidermal water loss tests were performed to characterize the biological in-vitro effects and ex-vivo results on pig skin (unpublished data).

From those tests, the authors concluded that the creams would not generate any occlusive effect after being applied on the skin, which, in theory, guarantees a lower risk of the bolus effect (receiving a large amount of radiation in a short time), stimulated by the ionizing radiation when the patient goes to the session having applied the product on the irradiated skin just before the radiotherapy.

Outcomes

The primary outcomes are the identification of radiodermatitis incidences and their classifications by degree, as well as the necessary time needed for the appearance of the first skin reaction secondary to radiotherapy exposition. As secondary results, the quality of life will be evaluated, as well as the reported symptoms and the variation in the temperature of the irradiated breast throughout the treatment (thermography).

Elegibility

The study will include women over 18 years of age with with healthy skin (without previous injuries) that will start radiotherapy sessions for breast cancer treatment

The exclusion criteria will be women:

- Having undergone previous radiotherapy sessions in the same region, or submitted to radical mastectomy surgery
- Receiving concomitant chemotherapy treatment
- Having a malignant neoplastic wound
- Being pregnant
- Having a history of collagen diseases, such as systemic lupus erythematosus and/or scleroderma
- Having dermatological conditions, such as psoriasis, bullous pemphigus, or epidermolysis bullosa
- Having visible inflammatory signs on the skin of the area to be irradiated
- Having a history of adverse reactions to the topical formulation components
- Currently using oral or topical anti-inflammatories
- Receiving some other type of intervention for the prevention of radiodermatitis not included in the standard skincare practices or the experimental protocol.

Randomization, blinding and recruitment

Participants will be randomly distributed into three groups. Randomization will be done in blocks of patients and will be stratified by the number of radiotherapy sessions using the statistical program R 3.5.1 (R Core Team, 2018; Viena, Austria). Thus, two lists will emerge; one for patients who receive 30 sessions of radiotherapy (group receiving a reinforcement dose, known as a boost) and another for patients who receive 25 sessions (group without a boost).

Patients will be recruited from the radiotherapy service through the radiation oncologist, who will indicate when a patient is a potential candidate for the study. The breast computed tomography schedule will also serve as a source of potential patients: on the day of the tomography, the main researcher will approach the potential patient, explain the objectives of the study, and invite her to participate, making it clear that she could be assigned to any group of the three available treatments. Once the patient agrees to participate, the inclusion criteria will be verified and the signature of the informed consent will be requested. Then, the first assessment and application of the data collection instruments will ocurr according to the study protocol (Fig 1).

Radiotherapy service protocol

All patients will follow the regular radiotherapy treatment protocol established by the Santa Casa da Misericordia Regional Cancer Hospital (philanthropic entity) in the city of Pasos, in the state of Minas Gerais, Brazil, which begins with a consultation with the radiation oncologist who collaborates with the technical staff and a professional in physics to define the treatment goals, total dose, position, focus volumes and organs at risk.

In the case of the present study, the treatment will consist of 25 sessions, in which the prescribed total dose of radiation will be divided within business days, excluding weekends. Patients will receive 50 grays (Gy) of ionizing radiation divided into 2 Gy per day. The patients previously submitted to conservative breast surgery will receive a 10 Gy boost dose in the operative area, during five extra sessions. In the case of lymph node involvement in the axilla identified after surgical removal of the nodules, the axillary regions and the supraclavicular fossa will be included in the treated tissue.

Before starting the treatment, patients will also have a consultation with a nurse where the general guidelines and prevention of the adverse effects of the therapy will be delivered and explained. Every five sessions, patients will have a medical consultation for reassessment (once a week).

Table 1. Name and function of each component of the creams used in the study

Components	Function
Liquid vaseline	Emollient
Isopropyl myristate	Solvent, emollient
Nipazole	Antimycotic (preservative)
Polawax	Thickener (emulsifier)
Lactic acid	Acidifying and antipruritic
Nipagin	Antimycotic (preservative)
Propylene glycol	Solvent
Purified water	Diluent
Nanoparticles with vitamin E	Active ingredient
Empty nanoparticles	Active ingredient

Intervention

Patients will be instructed to apply the cream on the area to be irradiated three times a day, approximately every eight hours (morning, afternoon and evening). This should always be done after the radiotherapy session, starting the night before the day of the first session to avoid applying the cream just before receiving the radiation. They will also receive instructions to follow the radiodermatitis prevention protocol with standardized skincare practices.

Radiodermatitis prevention protocol

The standard protocol includes general instructions to prevent the irradiated area from radiodermatitis:[4,8]

- Use water and a soap with neutral pH for gently cleaning the irradiated skin
- Keep the skin dry using soft towels and avoiding friction
- Use soft and loose clothes
- Protect the irradiated area from irritants

- Use accessories to protect yourself from the sun such as hats and shawls.

The protocols also suggest to avoid:

- Using deodorants, perfumes or cosmetics on the irradiated area
- Hair removal. If necessary, use an electric trichotomizer (shaver)
- Swimming in lakes, pools or the sea
- Taking hot baths or using saunas
- Using adhesives tapes and adhesives in general
- Applying thermal compresses (hot or cold)
- Sun exposure in the irradiated area
- Use of topical products with metals (zinc or aluminum).

Follow-up

Patients will be evaluated from the moment of inclusion in the study prior to the start of the radiation therapy program up to two weeks after the last session (Fig 1). The follow-ups will consist of an assessment three times a week (Monday, Wednesday and Friday) by the main researcher and by the radiation oncologist.

If the patient presents grade 1 or 2 radiodermatitis, the study protocol will remain unchanged, continuing the application of the cream, taking into consideration that the standard treatment of these lesions is the application of topical moisturizers, a function already performed by the cream under study.

If the patient develops grade 3 or 4 radiodermatitis, radiotherapy and the application of the cream under study may be suspended by the radiation oncologist until the skin lesion improves. The topical treatment of the lesions will depend on their characteristics following the institutional protocol. The patient should continue to apply the cream to the non injured irradiated regions.

Study settings

The study will be carried out in the radiotherapy service of the Santa Casa da Misericordia Regional Cancer Hospital, a reference hospital in oncology for all the municipalities in the southwest of Minas Gerais in Brazil. A three-dimensional conformal therapy (3D CRT) will be offered in the radiotherapy programs. It will be performed by two Elekta linear accelerators with a photon energy of 6 to 15MeV and electron energy of 4, 6, 8, 9, 10, 12 and 15MeV.

The aforementioned service has an average of 700 patients undergoing teletherapy and brachytherapy per year, applying 80 sessions per day. The most commonly treated cancers are prostate (25%) and breast (17%) cancers.

Population and sampling

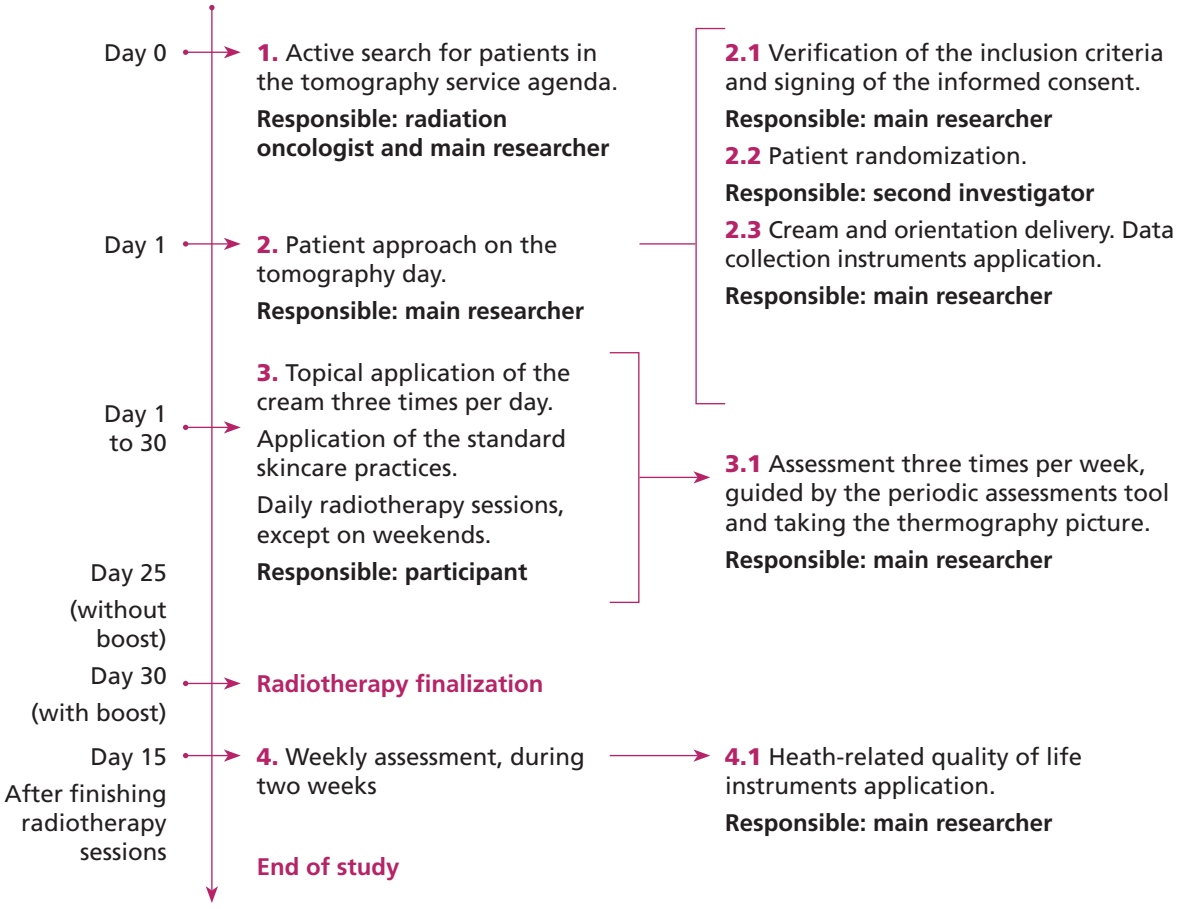
This project will focus on women with breast cancer undergoing radiotherapy. The sample will consist of 108 adult women with intact skin who agree to participate in the study. It will seek to achieve a power of 80% in the hypotheses tests and a significance level of 5%. The absence of published studies in the literature using the same active ingredient made it difficult to select and calculate an accurate sample. Therefore, a pilot study was carried out with 40 women (unpublished data) to serve as the basis for the definitive sample calculation using the G Power 3.1.9 program.[40,41]

Blinding

This study will have three types of blinding: patients will not know which treatment they will be assigned to, and neither will the researchers nor the statistician. The randomization lists will remain under the secrecy of a second researcher based in a different city to ensure that the sequence is not revealed, neither to the main researcher nor to the patients, before their inclusion in the study. Once the patient is included, the second researcher will virtually inform the corresponding treatment group to the main researcher.

Additionally, the three different creams will be packaged in 100g plastic tubes with the same characteristics, without identifying their composition on the label. The three creams will have the same color, consistency and texture, to prevent their differentiation. This will be achieved through the participation of a

Fig 1. Study protocol



pharmacist, who will prepare the creams in a licensed compounding pharmacy with experience in clinical trials.

To differentiate the treatment group in each tube, the label will indicate the mode of use in three different variations: topical use (group A), external use (group B) and external (group C). The pharmacy will be the safeguarded from blinding information about what treatment corresponds to each group until the end of the study.

Data collection

Four instruments will be used to collect the data and the information will be organized in a database coded in Microsoft Excel® (Microsoft, USA), which will be verified by a health professional not involved in the data collection process: The tools are described bellow:

- A sociodemographic and clinical data tool, including questions about the prescribed radiotherapy program

- An instrument for recording periodic assessments, including the physical evaluation of the irradiated skin, and the classification of acute skin reactions through two scales: Radiation Therapy Oncology Group (RTOG),[42,43] and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 from the National Cancer Insitute[44] (Table 2). This instrument also includes the Verbal Rating Scale (VRS) to assess pain intensity (1–10), pain location and duration; other symptoms in the last two days; the level of satisfaction with the cream (0–10) evaluated after every 10 sessions; complications; treatment interruptions and observations; and finally a checklist of compliance with the investigation protocol
- Quality of Life Questionnaire (EORTC QLQ-30)45,46 translated, culturally adapted and validated in Brazilian Portuguese.[47]
- Quality of Life Questionnaire Breast Cancer (EORTC QLQ-BR23)[45,47] translated,culturally adapted, and validated in Brazilian Portuguese.[48]

Along with the above-mentioned tools, a verification of the breast temperature will be carried out by taking a thermography picture as part of the instrument for periodic assessment. The thermography camera captures the infrared radiation emitted by the skin to map the temperature changes related to the alteration in blood flow. It is compatible with the inflammatory process present during the development of radiodermatitis and it is responsible for the erythema and the skin burning sensation.[49–51]

Skin thermography capturing analysis is an objective, non-invasive and safe measurement that does not interfere with the spontaneous course of patients' treatment. A thermography camera (Reveal Pro® Seek Thermal, Santa Barbara, California, United States) will be used to capture thermic images three times a week of the frontal, lateral and inframammary regions, always at the same time. Before taking the photograph, the patients will remain in the clinical office with a controlled room temperature for 15 minutes.

Statistical analysis

The quantitative variables will be described by the central tendency (mean or median) and scale (standard deviation interquartile range) measurements according to the data distribution. Meanwhile, the categorical variables will be described by the absolute and relative frequency. The comparison of the quantitative variables between the groups will be carried out with the ANOVA or Kruskal-Wallis hypothesis tests, as well as Fisher's exact test or chi-square for the categorical variables, depending on the data distribution. The R 3.6.1 software (R Core Team, 2019; Vienna, Austria) will be used, and a 5% level of significance ($p < 0.05$) will be considered.

Ethical procedures

The project was approved by the involved institutions (University of Sao Paulo School of Nursing and Santa Casa de Misericórdia de Passos Regional Cancer Hospital) obtaining the approval numbers 2.026.691 and 2.245.048. During the patients recruitment process, an informed consent format will be presented and explained, describing the study objectives and procedures. It will also mention patients' right to request information and/or stop participating in the study at any time. Each participant will have the opportunity of deciding to participate by signing the consent or not. A copy of the document will be available for each volunteer.

Conclusion

Radiodermatitis prevention in patients with breast cancer is highly relevant due to its effect on the health-related quality of life and the high potential impact of intervening with this problem,[3,11–13,52,53] since current literature is inconclusive and there is no consensus regarding this subject. The combination of a well known active ingredient (vitamin E) with a recently developed technology (nanotechnology) in response to the need for antioxidation in the development of radiodermatitis as part of its pathophysiology is a promising alternative. JWC LATAM

Table 2. Radiodermatitis grading instruments (RTOG and CTCAE v5.0)[42,43]

Scale	Grade 1	Grade 2	Grade 3	Grade 4
RTOG	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
CTCAE v5.0	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation in areas other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

RTOG: Radiation Therapy Oncology Group; CTCAE: Common Terminology Criteria for Adverse Events

Disclosures
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