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Photobiomodulation for the Prevention of Chemotherapy-Induced Peripheral Neuropathy: Randomized Clinical Trial Protocol

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ABSTRACT

Introduction: Chemotherapy applied as a breast cancer treatment may result in chemotherapy-induced peripheral neuropathy (CIPN) as a side effect, encompassing varying degrees of toxicity, according to the employed drug's pharmacokinetics, administration period, and cumulative dose. In this sense, photobiomodulation employing LASER or LED comprises a safe and non-pharmacological low-cost resource that has been widely studied for the mitigation and even resolution of various oncological comorbidities. The objective of this study is to evaluate the effectiveness of photobiomodulation employing a LED Therapeutic Display (LTD) in the prevention of lower limb CIPN in breast cancer female patients undergoing chemotherapy. **Methods:** This study encompasses a randomized double-blind superiority clinical trial including women aged 18 and over presenting breast cancer stages I to IIIC with indication for curative treatment applying neoadjuvant or adjuvant chemotherapy. Following recruitment, patients will be allocated into three groups: two intervention groups, which will undergo infrared and red LTD (A) and infrared, red, and violet LTD (B), and a control group (C), which will apply LTD with no light emission. The LTD applications will be conducted at home for 20 minutes daily on each plantar region, until the last day of chemotherapy. All groups will be assessed at the beginning of the chemotherapy treatment, during each cycle, and at the end of the treatment (at 30 days, 3 and 6 months). Lower limb CIPN incidence, pain, body balance, sensitivity, and quality of life will be evaluated, as well as LTD use satisfaction, treatment adherence, and CIPN impacts on daily living activities. **Results:** This study will evaluate the effectiveness of photobiomodulation employing LTD in preventing lower limb CIPN in Brazilian breast cancer female patients undergoing neoadjuvant or adjuvant chemotherapy. The results will encompass quantitative and self-reported patient data. **Conclusions:** This study is expected to demonstrate a new prevention modality for this breast cancer treatment complication.

KEYWORDS: breast cancer; peripheral nerve repair; photobiomodulation therapy.

INTRODUCTION

Breast cancer is the most common malignancy among women in Brazil, except for non-melanoma skin tumors[1]. Despite technological advances, adverse cancer treatment effects and chronic toxicities are still a challenge for healthcare teams[2].

Systemic therapy contributes to overall and disease-free survival based on the control of micrometastases presenting dissemination potential[3]. Chemotherapy involves administering antitumor chemical agents, either neoadjuvantly and/or adjuvantly. Neoadjuvant chemotherapy aims to reduce tumors to allow viable mastectomies and/or enable conservative surgeries. It is currently applied in early and locally advanced breast cancer cases, reducing the cancer stage and determining tumor responses to therapy. Adjuvant chemotherapy, on the other hand, aims at controlling remaining disease cells, lowering recurrence rates and improving long-term survival rates[4].

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Some known adverse chemotherapy effects include emotional, social, and self-esteem changes, functional loss, nausea, vomiting, fatigue, alopecia, mucositis, skin changes, and complications such as infections, peripheral neuropathy, febrile neutropenia, renal, hepatic, and cardiac toxicity[5].

Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common chemotherapy side effects and appears progressively during the chemotherapy. This condition is generally described as a bilateral and distal symmetric axonopathy generated by a drop in action potential amplitude and an increase in distal latency caused by deterioration of the peripheral nervous system, resulting in neural degeneration. CIPN can distort and/or interrupt reciprocal information from the central nervous system and the extremities of the body, often generating painful stimuli. The dorsal root ganglion, which plays an important role in the transmission of sensory signals, appears to be the main neural injury site, resulting in decreased cellular metabolism and axonal transport[6,7].

Motor symptoms typically manifest as distal weakness in the feet and hands, gait and balance disorders, and fine movement (writing, buttoning clothes, cutting, and sewing) difficulties. Sensory symptoms are represented as bilateral paresthesia, frequently reported as numbness, allodynia, neuropathic pain, and tingling in 90% of CIPN. Furthermore, a sensation of "wearing a thin sock or glove" is also common, as well as difficulty "holding things" and discriminating shapes, textures, and/or temperatures. These manifestations generally occur at the beginning of chemotherapy, between the first and third cycle, with peak severity occurring around the third month, leading to treatment delays due to pauses that might become necessary for tissue recomposition[7].

Some factors influence the incidence of CIPN, such as patient age, dose intensity, cumulative dose, chemotherapy duration, the co-administration of other neurotoxic chemotherapy agents, and pre-existing conditions, such as diabetes and alcohol consumption[8].

The ideal CIPN treatment, currently focused on controlling symptoms, has not yet been fully elucidated. In this sense, photobiomodulation employing low-power lasers is a safe, non-pharmacological, and low-cost resource that has been widely assessed for the mitigation or even resolution of various oncological comorbidities, and its use in CIPN cases has increased exponentially[9].

The light emission produced by a light emitting diode (LED) is a form of photobiomodulation, acting on capillary permeability and the synthesis of adenosine triphosphate in mitochondrial cells and of proteins such as collagen and elastin. LED devices can be used at wavelengths ranging from 405 nm to 940 nm. Biological responses to phototherapy, such as increased local blood circulation, cell proliferation stimulation, increased collagen and elastin synthesis, and adenosine triphosphate cellular energy modulation, are mainly affected by wavelength, providing an optional therapeutic resource to conventional treatments[10]. It is important to note that the use of LED-based devices is also beneficial concerning outpatient economy, as these equipments consume low amounts of energy and comprise lower-cost materials compared to light amplification by stimulated emission of radiation (LASER)[10].

The effectiveness of photobiomodulation employing LASER and/or LED therapy is also recognized as an effective intervention in breast cancer female patient cases for other clinical conditions such as dysgeusia, oral mucositis, lymphedema, and radiotherapy-induced dermatitis[11-13]. However, few clinical trials evaluating the effectiveness of photobiomodulation in preventing and treating CIPN are available to date[14]. The therapeutic pain control effect seems to be based on the mitochondrial mechanism of action, as described above, but also on the interaction of photonic energy with calcium ion pumps and cell membrane permeability modulation, allowing the balance of sodium and potassium ions across the cell membrane to rebalance the sodium-potassium pump[15-17]. Joy et al.[2] described a randomized pilot study evaluating photobiomodulation effectiveness in preventing breast cancer patient CIPN. The patients were divided into a control group (n=16) and an intervention group (n=16), receiving photobiomodulation applications twice a week during the entire chemotherapy treatment employing a LASER at two different wavelengths, 905 nm and 808 nm, at 4 J/cm^2. The authors concluded that patients in the intervention group demonstrated promising results in preventing symptoms related to peripheral neuropathy. Numbness in the extremities of the upper and lower limbs worsened significantly ($p<0.001$) in the control group, and a better quality of life was determined in the intervention group[2].

In this context, evaluating the effectiveness of photobiomodulation by employing LED Therapeutic Display (LTD) in preventing CIPN is paramount for the development of strategies that facilitate breast cancer control and its consequences within a Public Health System scope, comprising a low-cost and safe therapeutic proposal with significant clinical applicability.

Explanation for the choice of comparators

The participants in the control group (C) will receive the LED without light emission, capable of emitting the same audible alarms as the LED used in the intervention groups. In the first intervention group (A), red light and infrared LEDs will be applied, and in the second group (B), red, infrared, and violet light LEDs will be used. The three groups are necessary to obtain more reliable results and better understand the effects of different combinations of lights on preventing neuropathy, allowing us to compare the results with the control group, verifying whether the changes found in the other groups are actually due to the emitted lights or if they could occur due to other factors. When comparing groups A and B, we hope that the addition of violet light may provide complementary benefits or a greater enhancement to the effects of red and infrared light.

Research hypotheses

This study protocol describes a randomized superiority clinical trial encompassing breast cancer female patients undergoing chemotherapy in which the application of photobiomodulation through LTD in intervention groups A (red light and infrared LTD) and B (red light, infrared, and violet LTD) will be compared to a control group C (placebo). The study hypothesis is that the LTD applied to intervention groups A and B from the first day of chemotherapy is effective in preventing CIPN symptoms. The second hypothesis is that CIPN may be associated with worsening symptoms, such as pain, body balance, sensitivity, and quality of life.

Study objectives

Primary objective

The primary objective of the study is to evaluate the effectiveness of photobiomodulation employing LTD in preventing lower limb CIPN in breast cancer female patients undergoing chemotherapy at the National Cancer Institute, Cancer Hospital III (HCIII/INCA) – Brazil.

Secondary objectives

The secondary objectives of the study consist of evaluating:

- The incidence and clinical characteristics of lower limb CIPN after beginning chemotherapy according to the intervention group;
- Photobiomodulation effectiveness employing LTD in preventing lower limb CIPN;
- Photobiomodulation influences employing LTD on pain symptoms, body balance, and sensitivity, according to the intervention group;
- Health-related quality of life before and after chemotherapy and the presentation/development of neurotoxicity symptoms, according to intervention group;
- Photobiomodulation satisfaction and the impact of CIPN on daily living activities during chemotherapy.

Study design

This study comprises a randomized superiority clinical trial with three arms—two intervention groups and one control group—carried out in a reference breast cancer treatment center.

METHODS: PARTICIPANTS, INTERVENTIONS, AND OUTCOMES

Patients and study location

This study will be carried out at HCIII/INCA, in the city of Rio de Janeiro, Brazil, encompassing breast cancer female patients with indication for neoadjuvant or adjuvant chemotherapy.

Eligibility criteria

Women aged 18 or over presenting stage I to IIIC breast cancer with indication for curative treatment employing neoadjuvant or adjuvant chemotherapy at the HCIII/INCA will be included in this study.

Patients with a previous diagnosis of other primary cancers, who underwent surgery and/or chemotherapy to treat breast cancer at another institution, with previous feet sensation alterations, without the ability to respond to questionnaires, and unable to receive photobiomodulation due to acute lower limb infection will be excluded.

Treatment protocol/interventions

All patients will be evaluated by a physiotherapist, subjected to the first LTD application session and instructed to continue with the application at home from the first day of chemotherapy. All patients will receive a booklet with instructions for the correct use of the LTD and will be instructed to fill out an application frequency diary and continue with their usual physical activities.

The LTD applications must be carried out daily for 20 minutes on each extremity (soles of the feet), until the last chemotherapy treatment day.

Tissue from the extremities of the lower limbs will contact the LTD during its application in order to ensure uniform photobiomodulation administration (Figure 1).

Group A: Intervention group employing an LED red light (RL) and infrared (IR) board. Sequential LED treatments will be administered through a Sportllux Ultra LTD (Cosmedical) applying a predefined cycle, with a combination of light emitters at two wavelengths, namely 42 RL LED diodes (660 nm) and 42 IR LED diodes (850 nm); LTD measuring 10 x 12 cm; average power of each LED RL: 28.5 mW/cm^2 and IR: 23 mW/cm^2; operating mode: continuous; polarization: random; power density: 18.025 mW/cm^2; opening diameter of each LED: 1 cm^2; application time: 20 minutes; energy RL: 34.2 J/cm^2 and IR: 27.6 J/cm^2.

Group B: Intervention group with a red light, infrared, and violet LTD. Sequential LED treatments will be administered through a Sportllux Ultra LTD (Cosmedical) applying a predefined cycle, with the combination of light emitters at three wavelengths, namely 18 red light LED diodes (660 nm), 18 infrared LED diodes (850 nm), and 36 Violet LED diodes (420 nm); LTD measuring 10x12 cm; average power of each LED RL: 28.5 mW/cm^2, IR: 23 mW/cm^2, and Violet 52 mW/cm^2; operating mode: continuous; polarization: random; power density: 23.325 mW/cm^2; opening diameter of each LED: 1 cm^2; application time: 20 minutes; energy RL: 34.2 J/cm^2, IR: 27.6 J/cm^2, and Violet 62.4 J/cm^2.

Group C: Control group using an LTD with no light emission, using a Sportllux Ultra LTD (Cosmedical); LTD measuring 10 x 12 cm, and application time of 20 minutes.



Figure 1. LED Therapeutic Display used on lower limbs (on the soles of the feet) and application method.

Criteria for discontinuing or modifying the allocated interventions

The treatment will be suspended in case patients complain of sensory changes or pain in the CIPN-affected region following the LTD application. In the event of any other unforeseen changes, the healthcare team will assess the patients, and the necessary procedures will be adopted.

Strategies to improve adherence to interventions

Aiming at improving adherence to treatment, participants will receive a frequency diary to inform the dates they apply the LTD daily and whether it is being done to both feet for 20 minutes. This will be reassessed with each new chemotherapy cycle.

Relevant permitted or prohibited concomitant care during the trial

It is important to highlight that any other intervention by CIPN prevention study participants will not be permitted. Patients must carry out their normal routines, and the only interference in this study will be the application of the provided LTD.

Outcomes

First outcome

CIPN will be assessed by the Chemotherapy Induced Peripheral Neuropathy Assessment Tool (CIPNAT), at the beginning of chemotherapy, at each new cycle, and at 30 days, 3 and 6 months after the end of treatment. It contains 36 scored items in total, which evaluate the occurrence of symptoms, severity, distress, and frequency of peripheral neuropathy symptoms (sensitivity to cold, muscle and joint pain, numbness and tingling of hands and feet, loss of balance, weakness, and nerve pain), 14 items that assess interference with usual daily activities, ending with an open question about injuries resulting from the presence of symptoms. Patients will be asked about the development of each symptom since the beginning of chemotherapy. "No" responses receive a score of 0 and "yes" receive a score of 1 (score range 0–9). For each "yes" response, participants will answer additional items evaluating the severity, distress, and frequency of each reported symptom, employing a numerical scale from 0–10. Combining these three factors results in a total score range 0–270, with higher values indicating greater severity, distress, and frequency of the symptoms. The score for the group of symptom items experienced with added occurrences can range from 0–279. Higher scores on the symptom scale correspond to higher CIPN grades. Nineteen of the items are not scored in the CIPNAT, as they are described with the aim of obtaining information about the specific anatomical location of certain symptoms, the time of day when they occur most severely, and when the symptoms are most severe after the chemotherapy protocol. This questionnaire has been translated and validated into Brazilian Portuguese[18].

Second outcome

Secondary outcomes will be assessed before the beginning of chemotherapy, and at 30 days, 3 and 6 months after the end of treatment, as follows:

Pain: will be assessed using the short-form McGill Pain Questionnaire (SF-MPQ). This instrument initially asks patients about the presence of pain in the last seven days and, if so, its location. From there, sensory (1–11) and affective (12–15) pain characteristics are evaluated on a scale from 0–3 (absent, mild, moderate, and intense). A Visual Numerical Scale (VNS), in which the patient scores a pain intensity from 0–10, is also a part of the instrument. Finally, the patient is encouraged to identify his/her entire pain experience on a scale of 0–5 (no pain, minimal, uncomfortable, painful, horrible, excruciating). In the end, five scores are obtained: sensitive/sensory pain index (0–33 points), affective pain index (0–12 points), total index (sum of sensory and affective pain indexes), intensity of pain (0–5 points), and assessment of the entire pain experience (0–5 points). The final assessment will be calculated based on the frequency of patients who are sensitive and who present affective pain, pain intensity, and miscellaneous subgroups[19].

Body balance: the Timed Up and Go Test (TUG) aims to assess functional mobility and dynamic balance, scoring the risk

of falls when getting up, walking, turning, and sitting. Subjects sitting in a chair will be asked to get up and walk to a point on the floor, turn around and sit down in the chair again, and the time they complete this journey will be timed. Times of less than 10 seconds suggest individuals with mobility classified as normal; subjects with times between 10 and 19 seconds have good mobility, and patients who take 20 to 29 seconds are classified as regular mobility. Times of 30 seconds or more tend to reflect subjects with impaired mobility. Patients will be shown what the test consists of in advance and instructed to walk at their usual pace and speed. In case of doubt, the test will be repeated. For safety reasons, the examiner will walk alongside the patients during the test[20].

Sensitivity: will be assessed using an Esthesiometer (monofilaments). Patients will be evaluated in the supine position in a quiet and comfortable environment with as minimal interference as possible. The test will be demonstrated previously using a skin area with normal sensitivity; patients will be instructed to close their eyes; 10 points will be tested bilaterally on the lower limbs, totaling 20 points corresponding to the paths of the tibial, sural, saphenous, and deep peroneal nerves[21]. This technique is evaluated as described by Bell-Krotoski[22].

Health-related quality of life: a Brazilian Portuguese version of Functional Questionnaire Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-NTX) will be used. This instrument evaluates recent situations, referring to quality of life and neurotoxicity symptoms, totaling 38 questions divided into five subscales: a) Physical Well-being (7 questions; maximum score of 28 points); b) Social/Family Well-being (7 questions; maximum score of 28 points); c) Emotional Well-being (6 questions; maximum score of 24 points); d) Functional Well-being (7 questions; maximum score of 28 points); and Neurotoxicity Symptoms (11 questions; maximum score of 44 points). In this assessment, the interviewee is asked about recent information about their quality of life, functionality, and symptoms. If the answer is affirmative, meaning the item is a reality in their lives, they are asked to rate the intensity on a scale of 1–4. A total score is then obtained for each subscale and indices, indicating the relationship between them. The higher the score on each subscale and/or established indices, the better the patient's quality of life[23].

Satisfaction with the use of photobiomodulation: questions will be asked based on a semi-structured questionnaire about overall satisfaction and difficulty using the LTD, which will be classified as: I don't know how to answer, little, medium or very satisfied. Regarding changes in social life due to using the LTD, it will be classified as: no change, improvement, or worsening in social life. Changes at the application site such as pain, burning, discomfort, redness, itching, or the need to interrupt treatment, will be classified according to the Visual Analogue Scale (VAS), and the presence or absence of these symptoms.

Treatment adherence: will be checked using the LTD application diary, to be completed daily during the treatment period. In this diary, patients must inform the date of the LTD application, whether it was performed on both feet, and whether it lasted 20 minutes on each limb. The LTD application diary must be delivered on the last day of chemotherapy treatment.

Impact of peripheral neuropathy on activities of daily living: assessed using the CIPNAT. The participant who reports the presence of one or more symptoms in the assessment of the nine specific previously questioned neuropathic symptoms will be assessed by 14 items on the interference of these symptoms in daily activities. Interference in each activity is measured on a numerical scale from 0–10. The score in this set can range from 0–140, in which a high score indicates significant interference with activities due to neuropathic symptoms[18].

Patient monitoring

Patients will be evaluated in person at each new chemotherapy cycle and at 30 days, 3 and 6 months after the end of treatment. These reassessments will not bring any financial burden to patients as they will be carried out on the days and times during routine appointments.

Sample size

To calculate the sample size, with 80% power to detect a difference between groups of 1.1 for CIPN, considering a significance level of 5% and a loss percentage of 15%, in a one-tailed hypothesis test, a sample of 186 patients (62 per group) is required.

Recruitment

All patients who attend HCIII/INCA for their first chemotherapy consultation will be recruited to assess the study's eligibility criteria. Patients considered eligible will be informed about the objectives, treatment groups, adverse effects, and non-obligation to participate in the study. After agreeing to participate, they will be invited to sign an informed consent form, undergo an interview and physical assessment, and be randomized into the intervention or control groups. All patients will be evaluated and guided by the nursing team regarding skin care and symptom control before starting chemotherapy, according to the institutional routine. The study inclusion period will occur from March/2023 to June/2024 (Figure 2).

METHODS: INTERVENTION ALLOCATIONS (FOR CONTROLLED TRIALS)

Randomization

After recruitment, patients will be allocated into three groups: two intervention groups and a control group. The randomization will be carried out in a 1:1 allocation ratio for the three groups

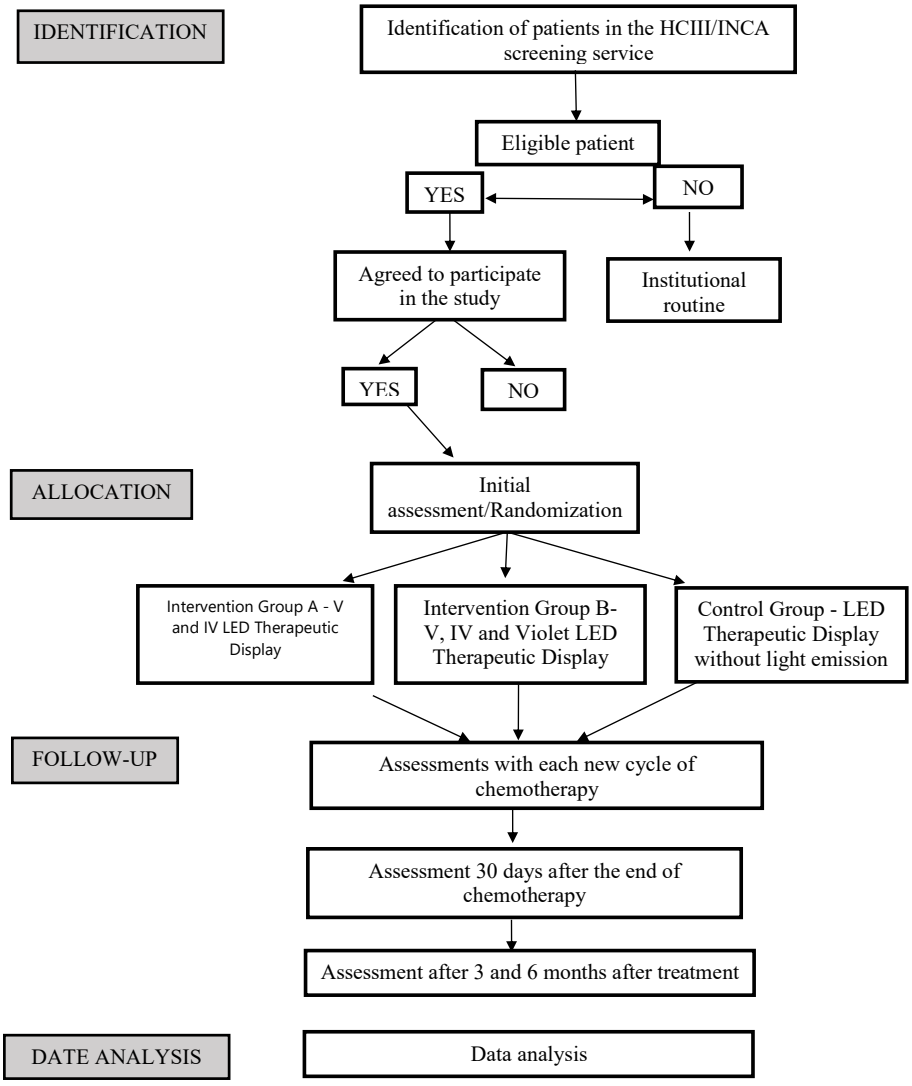


Figure 2. Recruitment and assessment flowchart. Infrared (IR) and Red (V) LED Therapeutic Display, and Infrared, Red and Violet (Sportllux Ultra Model) light. Placebo comparator: use of a LED Therapeutic Display with no light emission (modified Sportllux Model).

for every 15 patients, generated by a block of sealed and opaque envelopes with the following allocation codes: five codes for intervention group A, five codes for intervention group B, and five codes for control group C. Patients will be instructed on the use of the LTD and monitored during the chemotherapy period and up to 6 months after the end of treatment. All assessments, interventions, and data collection will be carried out by professionals trained and qualified for this purpose.

Blinding

Due to the nature of the intervention, physiotherapists supervising the application of the photobiomodulation technique will not be blinded. Only outcome assessors and patients will be blinded to group allocation.

To avoid a breach of anonymity, patients will be identified by a code and not by name or other form. Only the main researcher will have access to these codes and will assume responsibility for data confidentiality. All results will be presented together, consequently, no case can be recognized individually.

METHODS: DATA COLLECTION, MANAGEMENT AND ANALYSIS

Data collection

Data collection will be carried out by the study researchers through questionnaires, physical examinations, and clinical information collection from physical and electronic medical records, and stored in instruments suitable for research.

Variables regarding sociodemographic, clinical characteristics, lifestyle habits, tumor, and treatment characteristics will also be obtained from physical and electronic records.

Plans to promote patient retention and comprehensive follow-up

Participants will receive the necessary information at the time of recruitment to understand how the assessments will be performed and the importance of committing to complete the follow-up, including reassessments at each new chemotherapy cycle, and at 30 days, 3 months, and finally 6 months after the end of treatment. Any study participant may withdraw from the study at any time, without necessarily explaining the reasons. Patients will be monitored via telephone so that they may attend the physiotherapy department for assessment.

Descriptive and control variables

Variables related to the patient's characteristics will be used (age, skin color, marital status, education, occupation, and tobacco consumption), as well as clinical data (dominant side, independence in personal care, carrying out domestic activities, self-assessment of global health status, and comorbidities), condition of the skin of the feet (hyperemia, heat, wound, and edema), and tumor and oncological treatment characteristics (clinical staging, neoadjuvant or adjuvant treatment, histological type and grade, HER2, estrogen receptor, progesterone receptor, Ki67 receptor, date, side of surgery, type of breast surgery, breast reconstruction, axillary approach: sentinel lymph node biopsy, and/or axillary lymphadenectomy, number of removed and compromised lymph nodes, histopathological staging, chemotherapy, radiotherapy, hormone therapy and use of target therapy).

Data management

The data will be managed by physiotherapists who will fill out the information on sheets of paper. These will be kept in a safe place for a period of up to five years, in case of need for review or request by the Research Ethics Committee. The responsibility for filling in data in the electronic spreadsheet will rest with the same initial collectors. All data from the electronic bank will be reviewed and compared with paper forms before exporting to the program in which the analyses will be conducted, namely Statistical Package for Social Science (SPSS).

Data analysis

Statistical analyses will be conducted following the intention-to-treat principles.

Data normality will be examined using the Kolmogorov-Smirnov test, considering variables presenting $p>0.05$ as normal distribution. Descriptive analyses will be performed of the baseline characteristics for each group (A, B, and C). For continuous variables, central tendency and dispersion measurements will be carried out. The differences in means between groups for continuous variables with normal distributions will be compared using the independent samples T-test, while with non-normal distributions, the Mann-Whitney U test will be performed. Categorical variables will be described by relative and absolute frequency distributions and compared between groups through the chi-square test or Fisher's exact test, according to the number of individuals in the different categories of the analyzed variable.

Generalized linear models will be conducted, comprising tests based on longitudinal studies, based on a linear regression model of repeated measures between the three groups. The objective is to evaluate the association between photobiomodulation employing LTD and time (at the end of each chemotherapy cycle, and at 30 days, 3 and 6 months after the end of treatment) and the prevention of lower-limb CIPN, as well as the interaction between groups and time, in addition to their respective 95% confidence intervals.

The incidence of CIPN will be described by the cumulative incidence in all groups and within each group by a survival analysis using the life table method (at fixed times, namely at the end of each chemotherapy cycle and at the end of treatment). A subgroup analysis will be carried out with strong biological rationality and potential interaction effects. For subgroup C (control), quality of life will be compared through the FACT/GOG-NTX questionnaire before and after chemotherapy. We will also verify whether the effects of the placebo treatment interfere with the quality of life of these patients. All analyses will be carried out using the SPSS, version 20.0.

METHODS: MONITORING

Data monitoring

A data monitoring committee was not informed for this study. Therefore, research physiotherapists will conduct controls and notifications and assess possible adverse effects and symptoms that may be reported by patients. If adverse effects resulting from the intervention administered are observed, the participant may withdraw from the study, following an institutional routine where all necessary technical support will be applied.

Risks and benefits

Carrying out physical assessments may pose risks, although minimal, of possible sensory changes or pain when palpating the region affected by CIPN and some discomfort due to the pressure caused by the LTD application. Patients will be constantly monitored through in-person assessments and telephone contact, as, despite the low risks, allergic reactions such as skin irritation, itching, redness, minimal local superficial heat, and discomfort due to the pressure of the material on the skin during treatment may occur. If this does happen, patients will be referred for medical evaluations at the institution's emergency department.

Patients will not be remunerated for their participation, and this research may or may not offer direct patient benefits. By agreeing to the use of their information and/or material in

the manner described above, patients will be informed that they will not have any benefits or financial rights over any results from this research. The main benefit of participation will be that, in the future, the results achieved in this research may lead to a diagnosis and treatment for this type of alteration and benefit other patients. This research may or may not offer direct benefits to patients, as it is a study that is still in progress, so the following are expected as possible and potential benefits, according to current literature: CIPN prevention, pain improvement, functionality, and quality of life, enabling planning for actions to control complications.

Audit

No audits were planned or commissioned for this study.

ETHICS AND DISCLOSURE

Ethics

This study was approved on November 3, 2022, by the Ethics and Research Committee of the National Cancer Institute (CEP/INCA) under No. 5,737,539, in accordance with the attributions defined in CNS Resolution No. 466/2012 and CNS Operational Standard No. 001/2013.

This clinical trial is registered at ClinicalTrials.gov under the identifier NCT05663723.

Protocol changes

Any protocol modifications that may impact this study's conduct, potential patient benefits, or affect patient safety, including changes to the objectives, study design, population, sample sizes, and study procedures, as well as to significant administrative aspects, will require a formal amendment to the protocol. Such changes will be agreed by the authors and approved by the Ethics and Research Committee of the National Cancer Institute (CEP/INCA) before implementation and notified to the health authorities following local regulations.

Any administrative protocol changes that do not affect how the study will be conducted will be agreed to by the authors and documented in a memo. The Ethics Committee/CEP may be notified of administrative changes at the author's discretion.

Consent

Item not applicable, as this manuscript does not contain individual information or personal study participant data.

Confidentiality

The patients will be interviewed individually by trained professionals, in a calm environment, respecting established ethical-legal precepts, so that they feel comfortable answering the questionnaires. The collected data will be confidential and used without identification, where only the main researcher or some study researchers will have authorized access for use.

Disclosure Plan

This study protocol aims to answer whether the use of photobiomodulation is effective in preventing CIPN in breast cancer female patients. The results of this research will be published in scientific publications, at national and international events, and on other media portals. The study protocol will be presented to healthcare professionals and shared with patient groups through workshops and webinars.

Financing

The scientific expenses related to the publication and the Sportllux Ultra and modified Sportllux model LTD were covered by the company Bled Med Comércio e Distribuição Limitada (São Paulo, Brazil) through sponsorship and material donation. The remaining expenses are being covered by the researchers responsible for the study.

The authors declare that they have not received any financial support that could influence the content of this article. The principal investigators have no financial interest in conducting this study. This investigation was supported by the HCIII/INCA. The authors' interest is strictly for academic purposes.

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Declaration of interest

The authors declare that they do not receive any financial support that could influence the contents of this article. The principal investigators have no financial interest in conducting this study.

Data availability

No data was used for the research described in this article.

Auxiliary and experimental post-care

If an increase of over 10% is observed in adverse effects resulting from the interventions after the start of chemotherapy and patient inclusion in the study, the patient will be removed from the research and directed to continue the standard treatment offered at the Institution as per routine.

RESULTS

The results of this study will provide data based on quantitative, qualitative, and self reported responses from participants.

After analyzing the data, positive results are expected in the prevention of neurotoxic symptoms. This is the first study to evaluate CIPN prevention using LTD as an intervention. Planned follow-up will allow for short- and long-term data observations.

DISCUSSION

This study will evaluate the prevention of CIPN in Brazilian women with breast cancer through photobiomodulation using LTD, comparing red light and infrared LTD (group A), red light, infrared and violet LTD (group B), and LTD with no light emission (group C).

CONCLUSIONS

This study is expected to demonstrate a new prevention modality for this breast cancer treatment complication.

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AUTHORS' CONTRIBUTIONS

MCF: Conceptualization, Investigation, Writing – original draft, Validation, Writing – review & editing. EANF: Conceptualization, Validation, Writing – original draft, Writing – review & editing. RMC: Conceptualization, Validation, Writing – original draft, Writing – review & editing. DMT: Conceptualization, Validation, Writing – original draft, Writing – review & editing. SSA: Conceptualization, Validation, Writing – original draft, Writing – review & editing. JL: Conceptualization, Validation, Writing – original draft, Writing – review & editing. RRA: Conceptualization, Validation, Writing – original draft, Writing – review & editing. AB: Conceptualization, Validation, Writing – original draft, Writing – review & editing.

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