Cognitive Impairment in Treated Breast Cancer Survivors: Possible Approaches – a protocol for a randomized trial

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Abstract

Background: Throughout the last couple of years, significant advancements in cancer diagnosis and therapy have led to the identification of toxicities that impact patients' short- and long-term quality of life. Thus, we identify the cognitive dysfunction associated with cancer and its treatment, evaluating it both subjectively given the affected individual's viewpoint and objectively through the application of certain neurological tests.

Objective: The study aims to perform a prospective trial with three arms, comprising 120 non-metastatic breast cancer patients who received chemotherapy as a component of the curative efforts and were on hormone therapy at the time of enrollment.

Methods: The trial consists of identifying the presence of cognitive decline and following up on methods of preventing its accentuation through psychoeducation and cognitive stimulation. The trial includes longitudinal assessments of some subjective perception markers and objective assessments of cognitive decline. Furthermore, the study will delve into the dynamics of these markers, revealing alterations in the psycho-affective state.

Results: The project was approved in may 2024, and enrollment is not completed . The first results are expected to be submitted for publication in 2025.

Conclusion: The study aims to assess the significance of treatment approaches on the cognitive decline associated with cancer and its treatment, as well as the role they can play in improving breast cancer patients' quality of life.
Trial registration number: The protocol was approved by the Ethics Committee of UMF Iasi and was registered in Clinical Trials.gov Registry (NCT06662474).

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ABSTRACT

Background: Throughout the last couple of years, significant advancements in cancer diagnosis and therapy have led to the identification of toxicities that impact patients' short- and long-term quality of life. Thus, we identify the cognitive dysfunction associated with cancer and its treatment, evaluating it both subjectively given the affected individual's viewpoint and objectively through the application of certain neurological tests.

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Keywords: breast cancer, cognitive impairment, quality of life, intervention.

Introduction

Background

The improved survival rate of individuals with breast cancer is mostly due to readily available resources that allow for prompt and comprehensive diagnosis, as well as the availability of numerous superior therapeutic alternatives utilized in the treatment of this illness. In the present scenario, individuals who receive a diagnosis of breast cancer suffer cognitive impairments in varying proportions; therefore, it became important to characterize the cognitive dysfunction related to malignancy and therapy. The most common linked issues are difficulties with perception, attention, language, reasoning, remembering, and the ability to plan activities, comprehend, and solve problems [1]. Given the broad classification of conditions and the many methodologies used to evaluate them in previous research, epidemiological data are inadequate [2].

Risk factors

Individuals with malignancies located elsewhere in the central nervous system often experience cognitive impairments linked to cancer, typically during and after oncological therapy [3]. Despite research reports of alterations in cognition for short as well as long periods following oncological therapy, the duration of the time frame might range from 6 months to 20 years after treatment discontinuation. [4,5].

However, not every individual receiving the same type of treatment for the same illness subtype and stage has shown a decline in cognition, suggesting a link between the phenomenon and a number of related psychological aspects [6, 7, 8]. In addition to the occurrence of psychological aspects such as depression, anxiety, or exhaustion, individuals not yet receiving breast cancer treatment may exhibit cognitive impairment, a feature that may be associated with their age and educational level [9]. Cancer-related post-traumatic stress can lead to cognitive impairments prior to treatment [10]. For those undergoing active oncological therapy, difficulties may be associated with aging and intellectual reserve based on their educational background, job, and lifestyle [11, 12].

Those who started using treatment modalities report a greater incidence of cognitive deterioration in individuals who received cytostatic or hormonal therapy than those who only had surgery [13].

Despite the incomplete understanding of the mechanisms of chemobrain induction, research data mentions the actions of neurotoxic cytokines, which are a result of a sustained inflammatory

response and disorders in DNA repair [14].

Additionally, oncological therapeutic intervention might exacerbate natural processes such as aging. The aforementioned events are associated with oxidative damage and inflammatory processes, genetic information alterations, and decreasing telomere length [15]. Chemotherapy, acting on the same natural mechanisms, can exacerbate early aging signs, while hormone treatment exacerbates DNA damage due to a lack of antioxidant action [16, 17]. Oncological treatment, therefore, can trigger a sequence of biological processes that influence the initial deterioration in cognitive abilities, often subtle and intensified by age. It can also cause non-obvious early symptoms to become louder as the patient ages [18].
Genetic predisposition links polymorphisms of apoprotein E, catechol-O-methyltrasferase, and brain-derived neurotrophic factor genes to a higher incidence of neuropsychiatric involvement. The E4 allele of apolipoprotein E, a glycoprotein that helps neurons heal and change after brain damage, is linked to changes that happen in people with neurodegenerative diseases. Individuals who have already received chemotherapy for breast cancer carrying at least one E4 allele are more prone to impaired cognitive function compared to those without this allele [19]. COMT is responsible for metabolizing catecholamines through dopamine methylation and is involved in the development of cognitive disturbances associated with breast carcinoma therapy. Thus, homozygous patients with the Val-COMT allele metabolize dopamine more efficiently than those with the Met-COMT, resulting in a decreased level of dopamine in the frontal cortex. These characteristic influences patient’s results in attention tests, verbal fluency, and reaction speed [20].

Systemic therapy for non-metastatic breast cancer and cognitive impairment
Studies targeting cognitive disorders associated with breast cancer have evaluated cognitive decline in patients in the nonmetastatic stage. Thus, patients undergoing adjuvant treatment with chemotherapy have a higher rate of objective cognitive deterioration contrasting to individuals who skipped this type of treatment [21]. Also, the degree of cognitive impairment is proportional to the number of treatment cycles and administered doses [22, 23].
In the short term, research on cognitive function before, one week after the end of chemotherapy, and six months after reveals improvements after a 6-month recovery period that target spatial orientation, attention, delayed memory, and motor function. It seems, however, that after this time interval, the patients do not show improvement in executive function or immediate memory [24].
Studies on hormone therapy show that administering tamoxifen to patients who have previously received chemotherapy has a more potent negative effect on cognition [25]. The analysis indicates that, while chemotherapy has acute effects on cognition, these effects do not persist at the same intensity over the long term [25]. Compared to exemestane, people receiving tamoxifen as part of hormone therapy experienced worse executive function problems one year after starting adjuvant therapy. At the same time, there are no statistically significant differences between the results of patients treated with exemestane and the control group [26]. In terms of anastrozole, it causes cognitive decline in the first 6 months after its initiation, affecting memory, concentration, and executive function in both chemotherapy-treated patients and those who only received adjuvant hormone therapy. After six months, both patient groups' memory and concentration abilities improve, but a second decline in cognitive function begins to appear in patients who only received hormone therapy 12 months after treatment initiation [27].

Study rationale
A variety of pharmacological treatments and alternatives to medication are available to assist individuals with this condition.
Cognitive rehabilitation is one of the most well-represented. This entails routinely undertaking tasks to improve attention, response time, memory capacity, and executive function. Participants will

receive skills for memorizing, organizing, imagery, and association. Research has shown that these approaches, whether used in a structured environment or at home, are beneficial and yield benefits within a short timeframe of up to two months [28].
Physical activity is also involved in maintaining neurogenesis at the hippocampus level and preventing treatment-induced cognitive decline or depression in breast cancer patients [29, 30]. Practices such as meditation and mindfulness can improve short-term memory and processing speed in participants diagnosed with breast cancer [31].
Researchers have introduced pharmacological interventions into the study of cognitive dysfunction linked to malignancy and its management as a final possible therapeutic resource. Among the substances studied are some options that have proven beneficial effects, such as Modafinil [32], Donezepil [33], and Epoetin alfa [34].

Objectives
Many anticancer therapies are associated with cognitive issues.To integrate existing knowledge and enhance the quality of life for patients experiencing adverse effects of cancer therapy, further research and a multidisciplinary approach are required.The study's unique feature is that it assesses the influence of systemic pharmaceuticals (hormone therapy, chemotherapy) on neuropsychiatric functioning and quality of life in patients receiving active anticancer treatment. In conclusion, the selection of comparators took into account the necessity of implementing preventative actions tailored to the population's needs and acceptance, which can enhance quality of life and lessen cognitive decline.
Furthermore, the specific hypothesis posits that by engaging patients in the proposed intervention, their cognitive impairment will decline concurrently with an improvement in their psycho-emotional status. In this framework, a specific objective is outlined, suggesting that we can develop a range of potential interventions to enhance the observed outcomes, supported by selected tests to confirm their effectiveness.
Primary objective
The primary goal is to detect the presence of cognitive decline in breast cancer patients receiving systemic treatments. Additionally, we are interested in the rate of cognitive decline delay among those who implement prophylactic measures.
Exploratory objectives
Among the exploratory objectives, we want to evaluate the quality of life and psycho-emotional status of the patients included in the present study.

Trial design
The present research is a prospective, single center, with 3 arms study aiming to determine the cognitive impairment decline rate after 12 weeks of different interventions for each study group (Figure 1).

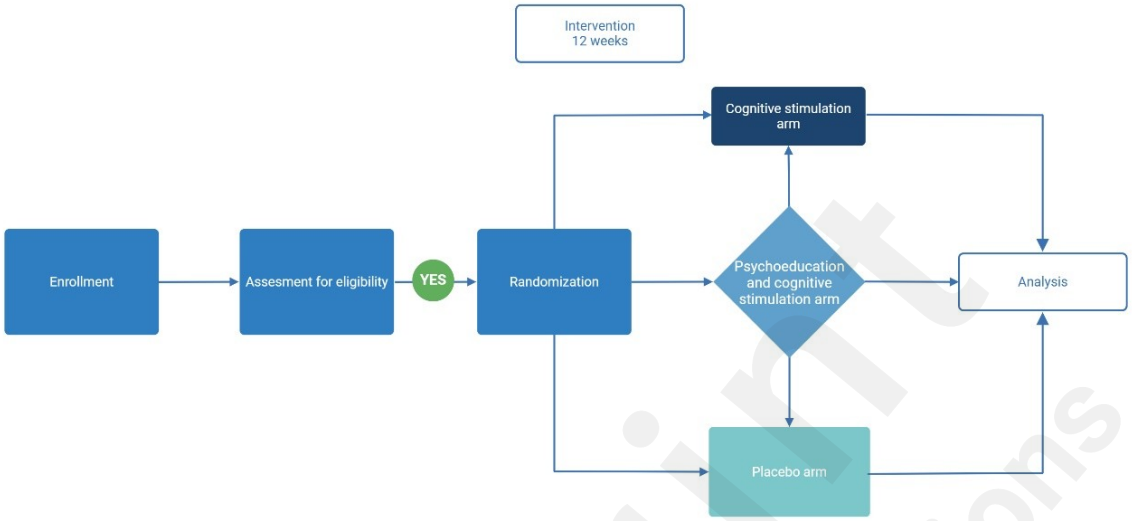

Figure 1. Flow diagram of the study

Methods

Eligibility criteria

Female patients aged 18 years or older with histologically confirmed treated invasive non-metastatic HR positive that provided written informed consent form are eligible to enroll in the investigation. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status 0 -2 and adequate hematologic functions. The patients must have completed the treatment (surgical intervention or chemotherapy) for at least six months and up to three years. before enrolling in the study. The study includes patients who have undergone chemotherapy for at least 3 months, including both dose-dense regimens and those administered every 3 weeks, as part of their disease treatment.

Exclusion criteria

We exclude patients with another carcinoma than breast neoplasia. In addition, it is necessary to exclude brain metastases at the time of inclusion in the study. Also excluded are patients diagnosed with acute neurological diseases, neuro-degenerative or major psychiatric conditions such as stroke, autism, ADHD, Alzheimer's disease, Parkinson's disease, dementia, obsessive-compulsive disorder, post-traumatic stress disorder, schizophrenia, and those with a history of craniocerebral trauma. Thus, we exclude patients with associated pathologies who may receive any form of treatment. The administration of psychotropic or pain medications in the II and III categories represents another exclusion criterion. Last but not least, people with performance status (ECOG) ≧3 or with laboratory tests that contraindicate the administration of active oncological treatment are excluded.

Study intervention

We randomly assign patients with a history of chemo-treated breast neoplasm, surgery, and hormonal adjuvant treatment to one of three subgroups, each with an indication to complete one of the related

12-week programs. To prevent cognitive decline, the first subgroup will engage in exercises like sudoku, word games, and painting by numbers for 30 minutes per day, three days weekly, for a duration of 12 weeks. Alongside the first group program, the second group will also hold open group meetings for psychoeducation (1 meeting every 2 weeks, 6 meetings in total). Group 3 is considered a control group, consisting of people who maintained their lifestyle up until their inclusion in the study without following additional measures.
Before the execution of the intervention, all those enrolled will have the necessary explanations. Thus, the investigators will ensure that each participant knows how to use sudoku, painting by numbers, and crosswords and will complete the investigation at home. Each participant from the first and second groups will have at their disposal the same number of sudoku sheets, crosswords, and sheets necessary for painting according to the numbers specified on the board, as well as the materials necessary to carry out these actions at home. The investigators provide these materials, which they will review at the end of the investigation to verify the performance of the proposed exercise. Additionally, specialized staff from the investigators' team will facilitate group sessions aimed at psychoeducation and cognitive stimulation for the participants randomly assigned to the second arm. These sessions will take place in an organized environment and adhere to a predetermined schedule.

The current study associates the discontinuation of the assigned intervention with the patient's withdrawal of consent, regardless of the patient's declaration of study-induced harms/personal requests without justification or the emergence of a progressive oncological disease or death.
The study team or participant cannot modify the allocated intervention at their will.
The research team anticipates that they may encounter difficulties related to participation during the course of the study, particularly those in the interventional arms. To improve our patients adherence, the proposed activities vary and are time-limited. These tasks are not time-consuming, and they will also be completed efficiently during routine visits.
The proposed intervention scheme includes activities patients will carry out at home, along with organized meetings that support the idea of comfort and intimacy. We schedule individual visits and organized meetings to help patients avoid unnecessary hospital trips. Therefore, to minimize the risk of patient no-shows, the research team should conduct all necessary additional testing during routine assessments. Regarding patient evaluation, the research team selected widely used and recommended tests for the study.
The present study does not define other concomitant actions that may be relevant for the outcome, and it does not prohibit them.

Outcomes
Primary outcome
This variable was chosen as the primary objective because it objectively demonstrates the presence of the cognitive dysfunction and how it varies during the course of the study. Objectively, we interpret a TMT part A result above 70 seconds and a TMT part B result above 273 seconds as pathological, indicating cognitive dysfunction of the subject. In addition, the change in the result by more than 13 (part A) and 20 (part B) seconds from the previous assessment is relevant for quantifying the evolution of the dysfunction. Additionally, the study will evaluate this variable consecutively to facilitate its interpretation in light of the changes brought about by the specified interventions.

Secondary outcomes
Subjectively, a FACT COG score below 60 is associated with cognitive dysfunction of the subject. In addition, a decrease in the score by more than 6.4 points compared to a previous assessment is considered a worsening of the dysfunction, and an increase by the same value is considered an

improvement.
The assessment also considers changes in quality of life during and after the intervention.
Regarding the psycho-emotional status of these patients, the scores resulting from the evaluations through the MAC (29 items scale) and DASS-21 R scales will help us characterize their evolution

Participant timeline
We are creating a database that includes general patient data, personal pathological and physiological antecedents of interest, educational level, tumor subtype, type of treatment, and whether the patient's treatment plan includes measures to prevent cognitive decline. The database will also contain the results of serial psychological, cognitive, and quality-of-life assessments.

During the first month (day 1 and day 28), we will evaluate the patients using Hamilton scales, which allow us to exclude from the study those who exhibit severe depression or anxiety based on this evaluation.

We will use the FACT-Cog (The Functional Assessment of Cancer Therapy-Cognitive Function) and Trail Making Test (TMT) for the objective study and personal perception of cognitive decline. We will use the EORTC QLQ-C30 (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire) to find out about the quality of life. The DASS-21R questionnaires (Depression, Anxiety, and Stress Scales) and the Mental Adjustment Scale in Cancer (29 items scale) will be used to find out about the mental and emotional state and how well the person is coping with the disease (Table 1. Study procedures).

Phases	Baseline/ screening	Treatment period	Follow-up	
	<30 days	Day 1- 12 weeks	3 months	6 months
Intervention		X		
Written informed consent	X			
Physical exam				
Complete clinical examination	X	X	x	x
Medical history	X			
Collection of concomitent treatments	X	X	x	x
Performance status	X	X	x	x
Laboratory examinations				
Hematology	X			
Serum	X			

chemistry				
Tumor evaluation	X			
Cognitive evaluation				
Hamilton Depression and anxiety rating scales	Day 1and 28	X	x	x
FACT-Cog, TMT, EORTC QLQ-C30, DASS-21R, MAC Assessment	X	X	x	x

Table 1. Study procedures

Patients are considered eligible for study continuation if, in 1 month of screening procedures, the tests to identify depression and severe anxiety do not indicate a severe status for them. Afterwards, the patients implement the prophylactic methods previously specified, based on their randomization subgroup. We carry out the first evaluation by applying the previously listed questionnaires at the end of the 12 weeks intended for the interventions.

Consequently, the patients will be evaluated 3 and 6 months after the end of the intervention period.

Statistical considerations

The study will include breast cancer patients undergoing systemic treatment, randomized 1:1:1 (40 patients in each arm) into 3 arms: placebo, carrying out prophylactic measures at home, or carrying out prophylactic measures at home and participating in group sessions with the general aim of psycho-education and cognitive stimulation. The block randomization method will randomly assign the patients to the three groups previously defined by the presence and type of prophylactic measures in the individualized treatment scheme. The outcome will be assessed through a variety of tests, being held under supervision by the investigators in a multidisciplinary team made up of oncologists and psychotherapists. Statistical analysis will then stratify the patients based on their age at study inclusion, the type of hormone therapy used, and the interval that had passed since the finish of chemotherapy.

The investigators will maintain the follow-up for the participants that discontinue or deviate from the protocol intervention if they maintain their consent.

Based on the literature data, we anticipate that both the first and second arm populations will experience improved outcomes. Additionally, these types of interventions demonstrated high responsiveness rates in multiple trials, but our understanding of the parallel evaluation of the first two interventions is limited.

Regarding data management, the study team will process the results statistically, ensuring anonymity. Only the individuals listed as the study team will have access to the results and study data. All personal data is confidential. The results derived from this study could be published for scientific purposes; it will not include the name or any other feature of personal information that allows

identification of the patient.

Ethical considerations

In the present study, the patient's involvement is voluntary, and she receives full details about the study's objectives, methods, time frame, safety , benefits, and potential distress. The information is provided both verbally and in writing. Informed consent was obtained from all subjects involved in the study. The informed consent is submitted in front of the investigator before enrolling and taking any study assessments. The consent forms are safely preserved, and every person involved receives a copy. During the enrollment process, each participant is assigned a number and a study name based on the initials of his surname and name.

The Regional Oncology Institute's ethics committee and the University of Medicine and Pharmacy's Research Ethics Committee 445/28.05.2024, respectively, approved the trial in April and May 2024. This protocol was registered in Clinical Trials . gov Registry (NCT06662474).

Results

This research received no external funding. The Research Ethics Committee at the University of Medicine and Pharmacy accepted the final protocol in 2024. We anticipate that participant recruitment will be finished by mid-2025 and that analysis will begin shortly thereafter. We plan to promote our findings through scientific publications and conference meetings, and we intend to make recommendations to health-related organizations.

Discussion

In recent decades, breast cancer survivors have enjoyed increased survival through improvements in early diagnosis and innovative treatments. We can identify a series of adverse effects in these patients that can affect their quality of life, including cognitive dysfunction.

Characterizing this toxicity, we can see that it affects perception, attention, and memory, as well as the ability to plan and solve problems [1]. Although its considerable influence on people with cancer, data on this toxicity is still limited [2].

Both the neoplastic disease and the treatment are responsible for these changes, but a number of factors predispose to the appearance of cognitive dysfunction. Therefore, psychological variables such as anxiety or depression, together with age and educational level, can impact cognitive decline [8, 9, 12].

Oncological patients may experience these changes over a shorter or longer duration, and both the use of chemotherapy and hormone therapy can contribute to these changes [11].

Starting from pre-existing studies that demonstrate the benefits of using certain methods to prevent cognitive dysfunction, the current trial aims to investigate the occurrence of cognitive decline and compare various resources to reduce its rate.

Furthermore, we are interested in assessing the quality of life and psycho-emotional status of the patients included in the research.

Given that breast malignancy survivors must endure the toxicity of curative treatments for an extended length of time, the investigation must be focused on appropriate and accessible ways to lessen these side effects [35].

With a rising spotlight on prophylaxis, current research trend is seeking to reveal particular drugs or practices that may have long-term advantages for cancer and treatment-related cognitive difficulties [36, 37].

The interventions applied to groups of randomized patients, which target individual actions at home or a combination of the mentioned with sessions for psychoeducation with specialized staff, highlight the current trial. The goal is to determine if this combination truly improves the psycho-emotional status and, ultimately, the quality of life.

Conclusions

Finally, we believe that after completing this study, we can identify certain interventions that can positively influence the lives of breast cancer survivors. We also believe that by evaluating the data, we will be able to identify the patients with cognitive impairment who benefit most from these activities.

Author Contributions

Conceptualization, D.I.P, M.O.,C.S., R.P., S.R.V. and L.M.; methodology, D.I.P., M.O.,C.S., R.P., S.R.V. and L.M; validation, D.I.P., M.O.,C.S., R.P., S.R.V. and L.M; formal analysis, D.I.P., M.O., C.S., R.P., S.R.V. and L.M; investigation, D.I.P., M.O.,C.S., R.P. and S.R.V.; writing—original draft preparation, D.I.P., S.R.V.; writing—review and editing, D.I.P., M.O., S.R.V. and L.M.; visualization, D.I.P., M.O., C.S., R.P., S.R.V. and L.M.;.; supervision, D.I.P., C.S., R.P., S.R.V. and L.M.;. All authors have read and agreed to the published version of the manuscript.

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