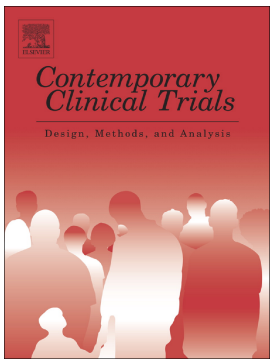

Cognitive remediation in breast cancer survivors: A study protocol

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PII: S1551-7144(25)00052-7

DOI: https://doi.org/10.1016/j.cct.2025.107858

Reference: CONCLI 107858

To appear in: *Contemporary Clinical Trials*

Received date: 24 June 2024

Revised date: 29 January 2025

Accepted date: 20 February 2025

Please cite this article as: P.A.R. Nunez, V. Gérat-Muller, C. Bellera, et al., Cognitive remediation in breast cancer survivors: A study protocol, *Contemporary Clinical Trials* (2024), https://doi.org/10.1016/j.cct.2025.107858

Cognitive remediation in breast cancer survivors: A Study protocol.

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Abstract

Cancer treatment-related cognitive impairment, also known as “Chemobrain,” is frequently reported among cancer survivors. This condition can persist for months after the end of cancer treatment and can affect various aspects of a patients’ quality of life. Despite growing evidence, research into effective treatments remains an emerging field. This project aims to assess the effectiveness of a cognitive remediation protocol called Oncogite in reducing cancer treatment-related cognitive impairment. The primary outcomes are self-reported functional and emotional well-being. The secondary outcomes include measures of executive function (working memory, inhibition, shifting), episodic memory, perceived cognitive

function and perceived quality of life. One hundred sixty-four breast cancer survivors will be recruited from an existing cohort. Patients will be randomized to either a cognitive remediation group or a no intervention group. Participation in the workshops will be via videoconferencing, led by a neuropsychologist. Patients in the experimental group will also have access to an internet platform with the exercises practiced between the group workshops. The intervention will last four months at a rate of one workshop per week. The following data will be collected: emotional and functional well-being, neurocognitive performance, switching, inhibition, cognitive complaints, episodic memory, fatigue and depression. We will conclude that the intervention is effective if there is 4-month improvement in both emotional and functional well-being to find in the experimental group in their cognitive functioning. This research will contribute to the development of new clinical tools for cancer treatment-related cognitive impairment and facilitate the return to work in cancer survivors.

Keywords

Cancer treatment-related cognitive impairment, breast cancer treatment, cognitive remediation, quality of life,

CRediT (Contributor Roles Taxonomy) statements

Pedro Alejandro Rodriguez: Methodology, investigation, writing - original draft, Véronique Gérat-Muller: Conceptualization, funding acquisition, methodology, Caroline Lalet: Data curation, Carine Bellera : Methodology, Formal analysis , Bruno Quintard: Writing – review & editing, Camille Chakiba: Writing - review & editing, Virginie Postal : Conceptualization, methodology, writing - original draft, funding acquisition, project administration

Background

Medical advances in cancer treatment have improved the life expectancy of patients [1]. This improvement has led researchers to express concern about the long-term adverse effects of cancer treatments on quality of life [2]. In particular, previous studies have recognized the presence of cognitive complaints in patients treated with chemotherapy [3]. Numerous studies have corroborated patients' complaints of cognitive impairment through neuropsychological assessments. Patients performed worse than control subjects in cognitive processes such as executive functioning, learning and information processing speed [3-12] .The spectrum of cognitive changes, universally known as “Chemobrain” has been progressively replaced by the term “cancer-therapy associated cognitive change” [13] .

However, the impact of treatment is still underestimated because the priority at the time of the cancer diagnosis remains the patient’s short- and medium-term survival; yet quality of life contributes to the long-term survival of cancer patients [14, 15]. Nowadays there are various treatment alternatives for managing cancer-therapy associated cognitive change. These include pharmaceutical treatments, primarily stimulants of the nervous system and medications used in patients with memory impairment, though their effectiveness varies among patients [16]. There are also non-pharmacological treatments such as physical activity and cognitive rehabilitation [17]. Cognitive rehabilitation, also known as cognitive remediation, involves repetitive tasks designed to improve specific cognitive processes [18]. Cognitive remediation has shown positive effects on verbal learning [17], perceived cognitive impairment [19], processing speed [20], working memory [21] and flexibility [22]. However, there is variability in the results, not all studies show the same benefits of cognitive remediation.

The Oncogite workshops are designed to meet the varying needs of cancer survivors. They are delivered via videoconference, are facilitated by a neuropsychologist and take place in a group with other breast cancer survivors. These exercises are also adapted to the level of

cognitive impairment of breast cancer survivors documented in the literature [23]. An initial qualitative assessment of this remediation protocol with 29 patients showed improvements in their perceived cognitive function and quality of life [24]. Therefore, there is a need for an in-depth assessment of this protocol to see if the benefits of this intervention can also be demonstrated in an objective cognitive assessment.

Objectives

The primary objective of this research is to evaluate the efficacy of a cognitive remediation program for breast cancer survivors, herein defined as patients who have completed their chemotherapy treatment. Efficacy will be measured by improvements in emotional and functional well-being, as well as enhancements in cognitive abilities and self-perceived cognitive functioning.

This clinical trial protocol follows the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines and is registered in a public trials registry (clinicaltrial.gov NCT05690828).

Materials and methods

Design

This is a multicenter, randomized, blinded controlled trial. Participants will be assigned to either the intervention group or a control group (waiting list) by a computerized randomization software named Tenalea. This software enables automatic randomization of participants based on stratification criteria, ensuring balanced distribution across defined

groups [25]. Randomization will be stratified based on two factors: Age (under 50 versus 50 or over) and the time elapsed between the end of chemotherapy and randomization (less than one year versus 1 year or more). Indeed, these variables are likely to influence the results. Firstly, age influences cognitive functioning in the general population, with evidence showing that non-verbal intelligence begins to decline progressively from the age of 20 [26]. It is therefore a variable that can potentially have an influence on the evaluations carried out in the study. Additionally, Lange et al. [5] highlights the role of age in the development of cognitive impairments in cancer survivors. Moreover, the incidence of cancer is higher among older adults [27]. Failing to stratify participants by age could result in disproportionate group distributions, potentially confounding the study's findings. Secondly, cognitive impairments related to chemotherapy can vary over time at different points in the treatment process [28], and can continue to change even after therapy ends [29]. For this reason, we considered it important to balance the groups based on this factor (Less than 12 months and more than 12 months) to ensure valid comparisons, knowing that we include patients between 2 and 24 months after treatment.

Participants

One hundred and sixty-four breast cancer patients will be recruited. The rationale for the sample size is detailed in the statistical analyses section. The main inclusion criteria are as follows: women aged 20–60 years with a diagnosis of non-metastatic breast cancer who have completed their chemotherapy cycle, 2 to 24 months prior to randomization. The main exclusion criteria include unstable psychiatric or neurological disorders causing cognitive impairment, a history of drug abuse, and difficulty understanding French.

Patient recruitment will take place at three cancer centers in France: Institut Bergonié, Comprehensive Cancer Center for Bordeaux and the French South Region (study sponsor),

Institut Universtaire du Cancer de Toulouse (IUCT, University Cancer Institute of Toulouse), and Institut de Cancérologie Strasbourg Europe (ICANS, Strasbourg Cancer Institute).

Procedure

Patient recruitment will be conducted by medical oncologists and psychologists at the participating centers. These professionals will present the study to patients who meet the inclusion criteria.

An initial assessment is conducted at the time of inclusion to measure emotional and functional well-being (FACT-B) [30], fatigue (FACIT-F) [31], general cognitive functioning (MoCA) [32], level of depression and anxiety (HADS) [33], vocabulary level (Mill Hill, part B) [34], updating and inhibition (TAP) [35], shifting (TMT) [36], the perceived cognitive functioning and its impact in quality of life (FACT-Cog) [37] and episodic memory with an original computerized task as used in Boujut [38]. Follow-up assessments are conducted at four months and again at eight months. The eight-month assessment for patients in the experimental arm will include additional questions about their satisfaction with the cognitive remediation program (see Figure 1). In the final assessment, participants will also be queried regarding potential COVID-19 infection, as the illness can cause short-term cognitive impairments.

[Figure_1]

Intervention

Participants randomized in the intervention group will attend weekly work group consisting of 10 to 12 participants to engage in the Oncogite program. This cognitive remediation protocol comprises various cognitive tasks aimed to enhance memory, executive functions, visual constructive abilities and language processes. Cognitive tasks' difficulty is tailored to match the specific impairments of breast cancer survivors as reported on literature [23]. Work sessions will be two hours long and they will be animated by a neuropsychologist using online support tools. Additionally, patients will have access to an online program called Oncogitiel. On this website, participants will practice with the exercises they learned on the weekly intervention. Tasks have different difficulty levels and patients can log in throughout the week. Over 30 exercises were developed to target different cognitive functions, with approximately six exercises designed for each function. Table 1 below provides examples of tasks categorized by the cognitive function they address.

Table 1 Cognitive Functions and Task Summaries

Cognitive function involved	Task summary
Divided Attention	Participants identify targets within a list of numbers while managing visual and auditory conflicts.
Visuospatial Memory	Participants must remember the location and color of squares marked on a 4x4 grid.
Flexibility	Participants alternate between sorting letters and numbers by answering specific keys.
Updating	Participants remember the color or shape of two steps backward in a sequence of shapes.
Inhibition	Participants see arrows on a screen and perform gestures indicating the opposite direction, requiring suppression of automatic responses.

Participants randomized in the control group will wait until the four-month assessment. After the initial four-month assessment, patients in the no-intervention arm will have the option to engage in the intervention on an individual basis, outside the formal study parameter

Outcomes

Primary outcome

The efficacy of the intervention program will be assessed based on a co-primary endpoint that includes both emotional (EWB) and functional well-being (FWB). EWB and FWB will be measured using the Functional Assessment of Cancer Therapy -Breast (FRENCH FACT-B) scales [30]. This questionnaire is appropriate for assessing quality of life because it was designed specifically for participants who have had cancer and has been used in several studies with this population [39-41].

The FACT-B self-administered questionnaire comprises 37 items and covers 5 domains of health-related quality of life: physical well-being, family/social well-being, emotional well-being, functional well-being, and areas of concern. The FACT-B has been validated for use in oncology clinical trials [30].

The EWB subscale comprises 6 items, each rated on a Likert scale from 0 (not at all) to 4 (very much). The total score for this dimension varies between 0 and 24 (the higher the score, the better the quality of life). A difference of 3 points or more will be considered clinically significant [42].

The FWB subscale comprises 7 items, each rated on a Likert scale from 0 (not at all) to 4 (very much so). The total score for this dimension therefore varies between 0 and 28 (the higher the score, the better the quality of life). A difference of 3 points or more will be considered clinically significant [43]. At four months, efficacy will be deemed effective if an improvement of 3 points or more is observed for both the EWB and the FWB scales.

Secondary outcomes

Additional quality of life measures will be evaluated using other subscales of the FACT-B including physical well-being, family/social well-being, and various issues of concern among breast cancer survivors.

Fatigue will be measured with the FACIT-F (Functional Assessment of Cancer Therapy - Fatigue) [31]. This subscale measures fatigue and its impact on daily activities and cognitive functions.

The general cognitive state is measured with the MoCA [32], designed to assess mild cognitive dysfunction, this scale evaluates attention, concentration, executive functions, memory, language, visual constructive abilities, abstraction, calculation and orientation.

Flexibility will be measured by the DKEFS: Trail Making Test [36] a modified version of the original Trail Making Test [44]. It comprises five conditions: Visual Scanning, Number Sequencing, Letter Sequencing, Letter-Number Switching and Motor Speed.

Updating will be measured by the 2-Back Task from the TAP [35]. A series of numbers is presented on the screen, the participant must decide if the number that is presented is the same as the one presented two steps earlier in the sequence. If the current stimulus is the same as the one presented two steps back, the participant must click on a button. If it is not the same, the participant must hold her response.

Inhibition will be measured with the Go/NoGo from the TAP [35]. In this task, the participant is asked to press a button each time a stimulus (letter “X’) is presented, if another stimulus (character “+”) is presented, the participant must withhold her response.

The perceived cognitive deficits and related quality of life will be measured through the FACT-Cog [37]. This questionnaire has 37 items and is answered through a 5-point Likert scale and has four subscales: Perceived Cognitive Impairment, Impact of Perceived Cognitive

Impairments on Quality of Life, Comments from Others and Perceived Cognitive abilities, this scale was validated on French population [45]

Vocabulary knowledge will be assessed using the Mill/Hill scale [34]. This scale consists of 34 items. An individual score thus ranges from 0 to 34, with a higher score indicating better vocabulary knowledge [34].

Anxiety and depressive symptomatology will be measured through the HADS [46] This scale is used to assess depressive and anxiety symptomatology. The French version of this questionnaire was validated in a population of patients hospitalized for cancer [33].

A computer task [34] will be used to assess verbal episodic memory. The task will examine the impact of executive functions (specifically shifting and updating) on the encoding of episodic memory. This task involves two parts (encoding and recognition), each consisting of three conditions (control, flexibility and updating). During the encoding phase, participants must read aloud words presented on the screen, then produce another word with the same first letter, with the condition of not producing a word of the same family as the word displayed on the screen, and not repeating a previous production or a previously displayed word. This task is performed during three conditions: For the Control condition, a correct response is to press the left button if the circle appears in the left frame, or the right button if the circle appears in the right frame. For the Flexibility condition, participants memorize the relationship between stimuli and assigned buttons. A correct response is to press the left button if the colored circle appears in the left frame, or the right button if the circle appears in the right frame. However, when the circle has a white outline, the location is irrelevant, and the participant must press the left button if the circle is blue or the right button if the circle is orange. Finally, for the update (1-back) condition, a correct response is given by pressing the left button if the circle appears in the same frame as the previous circle, or by pressing the right button if the circle

appears in the other frame. In all three conditions, the circles disappear one second after the response is given or remain for up to 5 seconds as long as there is no response. In the second part of the task, the recognition phase, participants are presented with words and asked if they remember having seen the word presented in the first encoding phase. The participants are also asked about features analogous to this learning according to the Remember/Know/Guess paradigm, which categorizes item recognition according to autonetic or noetic state of consciousness [43]. Some changes were made from the original task in order to adapt its difficulty level to our sample and better control lexical characteristics. Firstly, the number of words chosen per condition, 15 instead of 30 per condition. Secondly, no minimum response time is imposed for the encoding task responses. Finally, the list of words presented was modified in order to control for concreteness, imageability, frequency and emotional valence [48]. Performance on this task is determined according to the number of errors and the reaction time measured in milliseconds. All the questionnaires and tests are presented in Table 2.

Table 2 Assessment Measures and Cognitive Constructs

Assessment Tools	Subscale/subtests	Construct assessed
FACT-B [30]	Emotional Well-Being (EWB)	Health-related quality of life (HRQOL) in breast cancer patients.
	Functional Well-Being (FWB)	
	Social/Family Well-Being	
	Physical Well Being	
	Breast Cancer Subscale	
FACT-Cog [37]	Perceived Cognitive Impairments	Perceived cognitive functioning and its impact on quality of life
	Perceived Cognitive Abilities	
	Perceived Quality of Life	

	Coments from Others	
FACIT-F [31]	Fatigue	Self-reported fatigue
HADS [33]	Anxiety	Anxiety and depression
	Depression	
MoCA [32]	Visuospatial/Executive	Mild cognitive impairment
	Naming	
	Memory	
	Attention	
	Language	
	Abstraction	
	Delayed recall	
	Orientation	
Mill/Hill [34]	-	Vocabulary level
DKEFS- TMT [36]	Visual Scanning	Switching
	Number Sequencing	
	Letter Sequencing	
	Number-Letter Switching	
	Motor Speed	
TAP [35]	Go/No Go	Inhibition
	2-Back task	Updating
Episodic memory task [38]	-	Episodic memory

Other variables

In addition, variables such as the patient's socio-demographic status such as age, employment status, and social status will be recorded. Medical variables such as the type and date of treatments received. At the end of the study, the participant will be asked to rate their satisfaction with the Oncogite workshops.

Statistical analysis

Sample size

Efficacy of the intervention program will be assessed based on the main criteria: EWB and FWB, based on the FACT-B. Efficacy will be deemed effective if an improvement of 3 points or more is observed for both the EWB and the FWB scales [42, 43].

In order to highlight a difference in average EWB score of 3 points, assuming a standard deviation of 4.8, a 5% 2-sided type-1 error rate, and an 80% power, a total of 66 patients will be required (or 33 subjects per intervention group; t-test for difference in means). In order to highlight a difference in average FWB score of 3 points, assuming a standard deviation of 6.8, a 5% 2-sided type-1 error rate, and an 80% power, it is necessary to include a total of 164 patients (or 82 subjects per intervention group ; t-test for difference in means). Based on the most stringent assumption, a total of 164 subjects, i.e. 82 subjects per group are required.

Statistical analyses

Scores will be described by randomization group: mean score, standard deviation, as well as nonparametric statistics (min, Q1, median, Q3, max).

The average scores (primary and secondary) will be compared at four months between the two intervention groups (Student's t test), after ensuring that the normality assumption is not violated. Differences in mean scores will be reported with respective 95% confidence interval. Missing data will be handled according to the procedure described in the questionnaire scoring manual Scoring for each measure incorporates reverse scoring and prorating for missing data. Subscale scores may be prorated if more than 50% of the items are answered (e.g., 4 out of 7 items) using the average of the remaining responses. The total score is the

sum of the unweighted subscale scores [49] Analysis of primary scores will be conducted in the intent-to-treat population.

Other continuous endpoints (including scores) will be reported in terms of summary statistics that will include number of patients, median, minimum, and maximum, and additional percentiles if appropriate. Categorical endpoints will be reported in terms of counts and proportions.

Discussion

This study aims to evaluate the effectiveness of Oncogite, a cognitive remediation therapy designed to meet the needs of patients in the post-cancer period at the end of the anticancer treatment. The therapy offers several advantages including greater adaptability to the patient's schedule. The exercises are tailored to the magnitude and type of cognitive impairment reported in the literature. The intervention will be delivered in a team setting, which promotes cohesion and motivation to complete the workshops. The effectiveness of this intervention will be measured objectively and subjectively (self-reported). An improvement in the set of variables measured is expected in the experimental group, mainly in emotional well-being and functional well-being. These benefits are expected to be stable over time.

This initiative aligns with the objectives delineated in the French Ten-Year Strategy for the Fight against Cancer 2021-2030 [50]. The primary objectives of this initiative include reducing the long-term sequelae associated with cancer and improving the quality of life for patients. The present project complements other French national initiatives, such as the ALIZES program [51], which focuses on physical reconditioning, mobility, and emotional regulation or the BORA program [51], which targets cognitive rehabilitation post-treatment, offering small group sessions to improve attention, memory, and daily-life integration. Likewise, the Cancer and Cognition platform offers computer-assisted cognitive remediation

through adaptive sessions supervised by a neuropsychologist, targeting attention, memory, visuospatial processing, and executive functions [52]. Additionally, this study contributes to the ongoing efforts to assess the effectiveness of cognitive remediation programs, [19-22, 53-58], supporting and enhancing the development of programs tailored to the needs of cancer.

If effective, this protocol could be proposed to various networks of patients and therapists to benefit as many patients as possible. The Oncogite program could also serve as a tool for neuropsychologists to enhance their therapeutic offerings. By incorporating this structured cognitive remediation protocol into their practice, neuropsychologists can provide a new evidence-based intervention tailored to the specific cognitive deficits of cancer patients.

Similarly, if this benefit of the Oncogite cognitive remediation method is proven, future studies could be interested in evaluating its efficacy in other pathologies such as prostate [54] and testicular cancer [55], since cancer-related cognitive impairments have also been found in the latter.

Ethical approval

This research follows the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. This research received a French national ethics committee approval, CPP (Comité de Protection des Personnes) n °22.02671.000116.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Funding

This work is supported by Region Nouvelle-Aquitaine (APPR2021A-2020-11970710) 17/05/2021, the Ruban Rose Association (01/10/2018) and Klesia (07/04/2022). Sponsors did not participate in the study design, the collection, analysis or interpretation of the data.

Acknowledgements

We extend our gratitude to the following organizations for their contributions to this research: Instiut Bergonié, Association OnCOGITE, Malakoff Humanis, Association Francophone des Soins Oncologiques de Support, Institut Claudius Regaud, Instiut de Cancerologie Strasbourg Europe.

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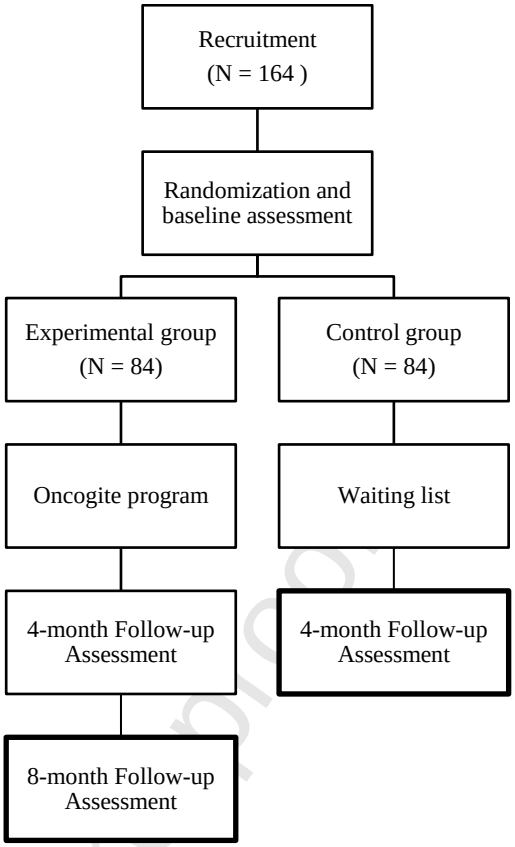

Figure. 1. Flowchart of study design and participants allocation.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The author is an Editorial Board Member/Editor-in-Chief/Associate Editor/Guest Editor for *[Journal name]* and was not involved in the editorial review or the decision to publish this article.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Highlights:

Internet delivered cognitive remediation may have a positive impact in both subjective and objective cognitive functioning.