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RESEARCH ARTICLE

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Neurotoxicity prevention with a multimodal program (ATENTO) prior to cancer treatment versus throughout cancer treatment in women newly diagnosed for breast cancer: Protocol for a randomized clinical trial

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Abstract

A current challenge in breast cancer (BC) patients is how to reduce the side effects of cancer and cancer treatments and prevent a decrease in quality of life (QoL). Neurotoxic side effects, especially from chemotherapy, are present in up to 75% of women with BC, which implies a large impact on QoL. There is a special interest in the preventive possibilities of therapeutic exercise (TE) for these neurological sequelae, and the benefits of TE could be improved when it is combined with vagal activation techniques (VATs). This superiority randomized controlled trial aims to

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examine the feasibility and efficacy of an 8-week multimodal intervention (ATENTO) based on moderate-vigorous intensity and individualized TE (aerobic and strength exercises) and VAT (myofascial and breathing exercises), on neurotoxicity prevention in women with BC before starting adjuvant chemotherapy (ATENTO-B) versus throughout adjuvant chemotherapy (ATENTO-T). A sample of 56 women newly diagnosed with BC, as calculated with a power of 85%, will be randomly allocated into these two groups. This study could provide an impetus for the introduction of early multimodal intervention methods to prevent neurotoxicity and consequently avoid the QoL deterioration that BC patients presently suffer throughout their treatments.

KEYWORDS

breast neoplasms, neurotoxicity, prehabilitation, quality of life, therapeutic exercise

1 | BACKGROUND

Quality of life (QoL) is a major concern in cancer care from the moment of diagnosis (Fernández de Larrea-Baz et al., 2020). Cancer- and cancer treatment-related side effects, namely neurotoxicity, have a negative impact on overall QoL. Neurotoxicity, which affects both the central and peripheral nervous system in 45%–75% of women with breast cancer (BC; Janelsins et al., 2014; Winters-Stone et al., 2017), is considered a sign of poor prognosis and survival (Goldstein et al., 2016) and could limit treatment completion (Stone & DeAngelis, 2016). Some patients show remission of these complications after treatments, but in up to 45%, they are present for several years (Huehnchen et al., 2020). Central and peripheral neurotoxicity in BC comprises a wide range of signs and symptoms, such as cognitive impairment, anxiety and depression, delirium, headache, cerebellar dysfunction, extrapyramidal disorders, tingling, numbness, and weakness (Stone & DeAngelis, 2016). Although its etiology is still unclear, several mechanisms of neurotoxicity have been proposed: chemotherapy-related mitotic inhibition (affecting neuronal function and survival; Hershman et al., 2014); the ability of some chemotherapeutic agents to cross the brain–blood barrier and directly damage central nervous system (Tanimukai et al., 2013); peripheral inflammation derived from tumor factors or psychological distress; and the increase in oxidative stress and mitochondrial dysfunction that activate the apoptotic pathway (Gordon-Williams & Farquhar-Smith, 2020). Moreover, neurotoxic symptoms co-occur with certain comorbidities such as psychological distress, fatigue, sleep disorders, and pain that exacerbates one another and reduces overall QoL (Chae et al., 2018; Hong et al., 2014). As a result, BC patients could develop a potent morbidity from the neurotoxicity that, in turn, worsens their prognosis. Therefore, they require a powerful, comprehensive intervention.

Therapeutic exercise (TE) has positive effects for cancer prevention (Jones, 2015), relief of symptoms (Cormie et al., 2017), and improvement of survival (Morishita et al., 2020). For example, the effects of exercise on the nervous system have been widely studied, namely inducing neurogenesis as well as influencing the cellular proliferation of the dendrites, which help to prevent neurodegenerative diseases. In addition, preclinical studies suggest that TE could prevent neurotoxic symptoms, such as cognitive impairment, by improving hippocampal plasticity and mitochondrial function (Park et al., 2018). Likewise, TE seems to enhance the effectiveness of chemotherapy and radiotherapy (Schadler et al., 2016), improving medication perfusion and patient immune cell infiltration through modification of the vascular network surrounding the tumor (Aschcraft et al., 2019). In particular, there is strong support for the efficacy of TE during and after cancer treatment in women with BC in terms of QoL improvement, central and peripheral neurotoxicity in terms of cognitive impairment, anxiety and depression symptoms, and numbness and tingling (Campbell et al., 2020; Mishra et al., 2012; Streckmann et al., 2014). Therefore, is an urgent need for TE to be adapted to the condition of the individual patient since excessive doses are counterproductive (Jones, 2015). Two strategies have been proposed to objectively regulate TE: (i) measurement of heart rate variability, an index of autonomic nervous system function, that reflects the interplay of the sympathetic and parasympathetic nervous system (Coumbe & Groarke, 2018); (ii) m-health devices to monitor the recovery of patients in real-time after sessions (Medina Quero et al., 2017), which has an important role in prevention and rehabilitation programs (Debon et al., 2019).

In parallel, the use of vagal activation techniques (VATs; such as myofascial and breathing exercises) may reinforce the benefits of TE. Some authors highlighted the importance of stress reduction to avoid inflammatory and hormonal responses resulting in neurotoxicity in oncological patients (Lacourt & Heijnen, 2017). As stress reduces parasympathetic activity, interventions targeted at improving vagal function are recommended for reducing inflammatory status (Woody et al., 2017).

Emergent research proposes to explore multimodal interventions (i.e., TE plus VAT) before BC treatment to reduce short- and long-term sequelae. The combination of both TE and VAT could be a powerful option for these BC patients, but its efficacy has not yet been studied. Considering the positive dose–response relationship between exercise intensity and beneficial outcomes, high-intensity exercise has been suggested (Campbell et al., 2020). Prehabilitation may physically prepare these patients for cancer treatment and may benefit their long-term

health and QoL (Giles & Cummins, 2019). While the theoretical bases of prehabilitation are well established, it is unknown whether the development of these multimodal programs is more effective before the beginning of adjuvant chemotherapy or throughout this treatment in terms of neurotoxicity prevention. Therefore, we designed the protocol "Adjusting the Dose of Therapeutic Exercise to Prevent Neurotoxicity Due to Anticancer Treatment (ATENTO)," to examine which phase would be more effective for preventing QoL deterioration through prevention of cancer treatment-related neurotoxicity.

1.1 | Objectives of the present study

The main objective of this study will be to analyze the effect of a multimodal program on overall QoL through prevention of neurotoxicity in women with BC when the program is performed at two different time-points: before (ATENTO-B) or throughout (ATENTO-T) adjuvant chemotherapy. The specific objectives are as follows:

- To assess and compare the effects of ATENTO-B versus ATENTO-T on QoL, clinical variables, and physical variables for BC at the end of adjuvant chemotherapy, at 6-month follow-up, and at 12-month follow-up.
- To examine how changes in clinical and physical variables related to neurotoxicity affect changes in QoL outcomes in women with BC.

We hypothesize that women who perform the ATENTO-B multimodal program will have better QoL and lower neurotoxicity than those women who perform ATENTO-T.

2 | METHODS

The methodology for this study will follow the directives from the SPIRIT 2013 Statement (standard protocol items: Recommendations for interventional trials) and from the Consolidated Standards of Reporting Trials statement (Figure 1). This trial has been approved by the Institution's Committee of Biomedical Research Ethics and follows the principles of the Helsinki Declaration (2013 version). The study will be carried out in accordance with the data protection law (3/2018).

2.1 | Design

The ATENTO study is a single-blind, two-armed, superiority randomized controlled trial.

2.2 | Participants, recruitment, and setting

Eligible patients will be recruited from the institution's breast unit by three surgeons and the nurse in charge at the time of diagnosis, following the criteria described below. After receiving general information about the study in the hospital, patients will be contacted by a researcher to make an appointment and perform baseline assessment (*t*0) 2–4 days after BC diagnosis. All participants will be informed verbally and in writing, and written informed consent will be obtained before performing assessments.

Women will be included in the study if they accomplish the following inclusion criteria: (a) age between 18 and 70 years, (b) having a BC diagnosis (Stage I–III), and (c) on the waiting list for adjuvant chemotherapy with risk of central and peripheral neurotoxicity (chemotherapy based on anthracyclines or taxanes regimen). Exclusion criteria are (a) having a previous history of cancer or any cancer treatment, (b) pregnancy, (c) participating in another intervention that could influence on the outcomes (e.g., TE, body-mind therapy) or (c) having a neurodegenerative disease that affects the central or peripheral nervous system and could influence the results.

2.3 | Data collection

Assessments will be conducted at baseline between 2 and 4 days after BC diagnosis (*t*0), 1 or 2 weeks after adjuvant chemotherapy for BC (*t*1), at the 6-month follow-up (*t*2), and at the 12-month follow-up (*t*3). The endpoint measures are detailed below. All of these assessments will be carried out by a single researcher with more than 3 years of experience in the facility. We will divide the assessment protocol into 2 separate days to reduce participant burden. All assessments will take place at the same time of day. Table 1 provides the assessment schedule and data collection time points.

2.4 | Measures

2.4.1 | Quality of life

QoL will be measured using the *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) version 3.0* (Aronson et al., 1993). This tool is composed of five functional scales, three symptom scales, a global health status/QoL scale, and six single-items. Responses range from 0 to 100, where higher scores represent better QoL (Fayers et al., 2001). The EORTC QLQ-C30 is a reliable measure with a Cronbach's alpha for global QoL subscale of 0.89 (Aronson et al., 1993).

2.4.2 | Central neurotoxicity

The *Trail Making Test* (*TMT*) will be used to assess mental flexibility, speed of processing, and executive function. The TMT consists of two parts: in Part A the subject draws lines sequentially connecting numbers from 1 to 25 as fast as possible; and in Part B the subject draws lines to connect the numbers numerically and the letters alphabetically as fast as possible, alternating numbers and letters in

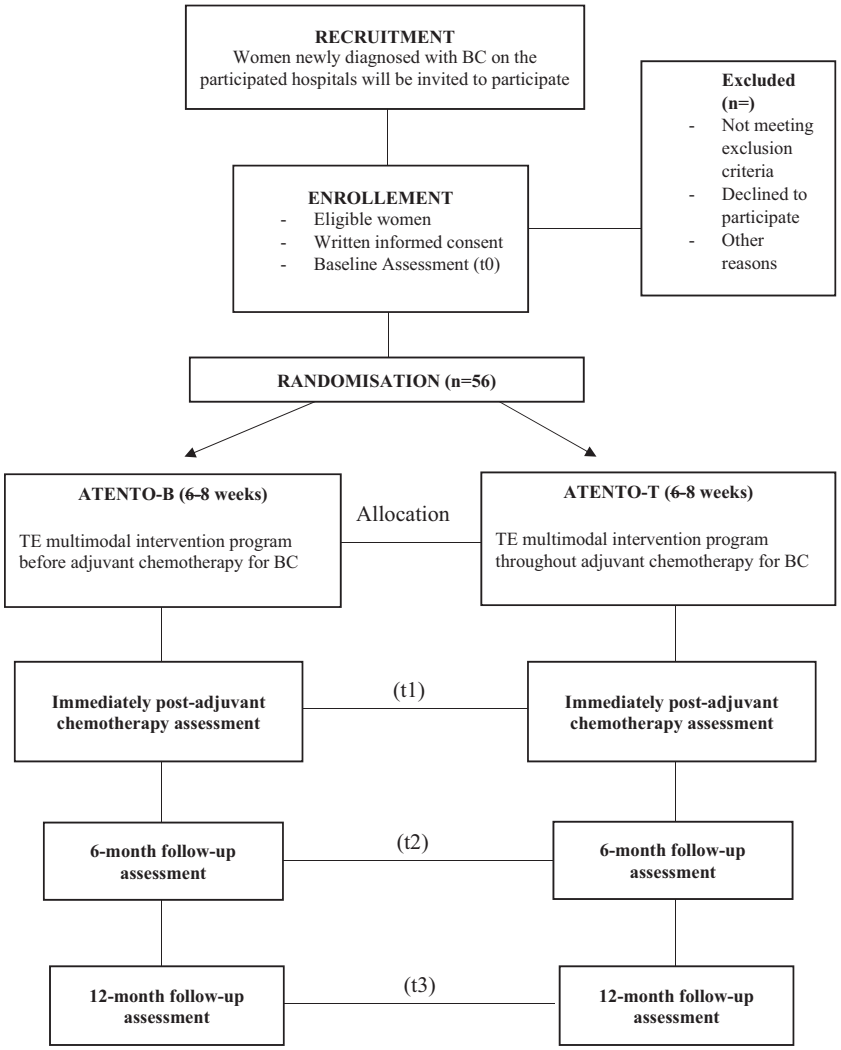

FIGURE 1 Flow diagram of ATENTO study. BC, breast cancer; TE, therapeutic exercise

consecutive order. The time spent on both tasks is noted. The total completion time for Part B minus the total completion time for Part A is used as an indicator of cognitive flexibility. A smaller B − A difference (s) indicates better cognitive flexibility (Tombaugh, 2004).

Memory and cognitive processing speed will be measured using two of the four score indexes from the *Wechsler Adult Intelligence Scale* (Wechsler, 2008): the Working Memory Index (WMI) (composed of the digit span and arithmetic subtests) and the processing speed index (PSI) (composed of the symbol search and coding subtests). The WMI and PSI have demonstrated high reliability (Cronbach's α: 0.94 and 0.90, respectively; Watkins, 2017).

2.4.3 | Peripheral neurotoxicity

The *EORTC QLQ-Chemotherapy-induced peripheral neuropathy* (*QLQ-CIPN20*) will be used to assess neuropathic symptoms (Postma et al., 2005). This tool is composed of 20 items scored from 0 to 4 classified into three subscales: sensory, motor, and autonomic symptoms. Higher scores indicate a greater presence of symptoms. The CIPN20 has Cronbach's α coefficients ranging from 0.78 to 0.88 (Kieffer et al., 2017).

Semmes-Weinstein monofilaments (*SWMs*) will be used to detect peripheral sensory neuropathy (Bell-Krotoski et al., 1995). They will be used on 14 points on the hands and feet (right and left). Monofilaments will be applied in order of stiffness, three times per point. The first monofilament (the thinnest) the patient feels at each point of application will be noted. SWMs are a valid tool for identifying subclinical peripheral neuropathy in cancer (da Silva Simão et al., 2014).

2.4.4 | Other general variables

The *Hospital Anxiety and Depression Scale* (*HADS*) will be used to assess such symptoms (Zigmond & Snalth, 1983). It consists of 14 items scored from 0 to 3 and grouped into two subscales: anxiety and depression. The HADS has a Cronbach's α of 0.90 for the full scale, 0.85 for anxiety, and 0.84 for the depression subscale (Herrero et al., 2003).

TABLE 1 Data collection timepoints and study scheduled

	Study period							
	Postdiagnosis			Before treatment	Throughout treatment	1–2 weeks posttreatment	6-month follow-up	12-month follow-up
Enrollment	Baseline	Allocation						
Timepoint	–	*t*0	–	ATENTO-B	ATENTO-T	*t*1	*t*2	
Enrollment								
Eligibility screening	X							
Informed consent	X							
Allocation			X					
Interventions								
ATENTO-B				←	→			
ATENTO-T					←	→		
Assessments								
Quality of life		X				X	X	X
Central neurotoxicity		X				X	X	X
Peripheral neurotoxicity		X				X	X	X
Anxiety and depression		X				X	X	X
Fatigue		X				X	X	X
Pain		X				X	X	X
Quality of sleep		X				X	X	X
Cardiorespiratory fitness		X				X	X	X
Static body balance		X				X	X	X
Physical activity level		X				X	X	X
Body composition		X				X	X	X

The *Piper Fatigue Scale-Revised* (*PFS-R*) will be used to assess cancer-related fatigue (Piper et al., 1998). The PFS-R consists of 22 self-report items that are scored from 0 to 10 points and grouped into four subscales (behavioral, emotional, sensorial, and cognitive subscales) and a global index, in which higher scores indicate the greater impact of fatigue. This scale has been validated in Spanish BC patients obtaining satisfactory reliability and validity values (Cronbach's α: 0.87–0.94; Cantarero-Villanueva et al., 2014).

The short form of the *Brief Pain Inventory* (*BPI*) will be used to assess pain severity and the interference of pain with daily activities (Poquet & Lin, 2016). The BPI consists of four items for severity and seven for interference. The scores range from 0 (no pain/no interference) to 10 (worst imaginable pain). The BPI has a Cronbach's α ranging from 0.87 to 0.89 (Badia et al., 2003).

Pressure pain thresholds will be used to explore the quadriceps, deltoid, trapezius, and cervical muscles bilaterally using an algometer. Each point will be stimulated three times, and the mean value for each one point will be considered. The examiner will instruct patients to warn when the pressure sensation changes into pain. Algometry has been demonstrated to be reliable (intraclass coefficient correlation [ICC] = 0.91; Chesterton et al., 2007).

The *Pittsburgh Sleep Quality Index* (*PSQI*) will be used to evaluate sleep quality (Buysse et al., 1989). It consists of 19 self-reported items and five questions reported by a roommate not considered for the analysis. Items are grouped into seven subjective dimensions: quality, latency, duration, efficiency, disturbances, medication use, and daytime dysfunction. Each item is scored on a 0–3 scale, with a total score ranging from 0 to 21 where higher scores indicate worse sleep quality. The PSQI is a reliable tool in cancer (Fontes et al., 2017).

2.4.5 | Physical variables

A cardiopulmonary exercise test will be performed with a *Medisoft, 870 A treadmill and Jaeger MasterScreen® CPX gas analyser* to assess peak VO_2 according to the protocol of the University of Northern Colorado Cancer Rehabilitation Institute. The protocol includes twenty-one 1-min exercise stages. This protocol is a valid method for establishing peak VO_2 (Kee Shackelford et al., 2017).

We will use the *Flamingo test* to assess whole-body balance. The test consists of balancing on their preferred foot with the free leg flexed at the knee and the foot of this leg held against the buttocks. The that the subject is able to hold this position for up to 30 s is noted. The average of both legs will be used in the analysis. Lower scores indicate better whole-body balance (Nàcher Roig et al., 1998). This test has shown good reproducibility with an ICC of 0.82 (Vancampfort et al., 2019).

2.4.6 | Physical activity level

One of the short forms of the *International Physical Activity Questionnaire* (*IPAQ*) will be used to measure the physical activity or inactivity level (Craig et al., 2003). It includes seven open-ended questions relating to physical activity in the last week. The IPAQ is a reliable tool in cancer patients (Ruiz-Casado et al., 2016).

2.4.7 | Anthropometrics

We will use an *InBody 720* impedanciometer that estimates lean body mass, fat mass, abdominal adipose tissue, and body max index (kg/m^2) and provides reliable results (Thomas et al., 2001).

2.4.8 | Additional parameters

Sociodemographic and clinical data will be collected with a self-report questionnaire. Stage of cancer, history of cancer and relationship, treatments received, and treatment reductions or interruptions will be recorded via a mobile app (ATOPE+) developed by our research team (https://www.safecreative.org/work/2010285737407-atope). The ATOPE+ app will also be used to record data about TE session's modifications and adverse effects.

2.5 | Randomization and blinding

After baseline assessment (*t*0), randomization will be performed by an independent researcher using a computer-generated number (EPIDAT 4.2 Xunta de Galicia). The program distributes each number to one of two lists, one for the ATENTO-B group and the other for the ATENTO-T group. The allocation of each participant will be known by the researcher who will carry out the intervention. Data analysis will be performed by a blinded researcher (M. A. M).

2.6 | Intervention

All participants of this study will perform the ATENTO program but in different timing: before (ATENTO-B) or throughout (ATENTO-T) adjuvant chemotherapy (see Figure 2).

ATENTO is a face-to-face, multimodal 8 weeks program. ATENTO is based on TE combining supervised individual aerobic and strength exercises, following VAT at the participating institution, and a home-based physical activity promotion using a steps per day strategy (Tudor-Locke & Bassett, 2004) monitored with FITBIT activity bracelets (Inspire, HR, Fitbit). The intervention will be conducted and supervised by a specialist in TE who will ensure the correct execution and adaptation of all exercises for each patient. Implementation processes and adaptations will be recorded by the intervention checklist to guarantee fidelity. For the first 2 weeks, the main objective will be to improve general physical health and to correctly execute each exercise. After this, more specific physical exercises will be used. A nonlinear prescription (with daily load and frequency of sessions per week) will be determined with a mobile app (ATOPE+; Moreno-Gutierrez et al., 2021), according to FIIT (frequency, intensity, time, and type) parameters (Campbell et al., 2019); see Table 2 that shows the ATENTO program in detail. The intensity of the aerobic and strength exercises will be controlled according to heart rate (Nilsen et al., 2018) and perceived exertion (Garnacho-Castano et al., 2018). Each session will have three parts:

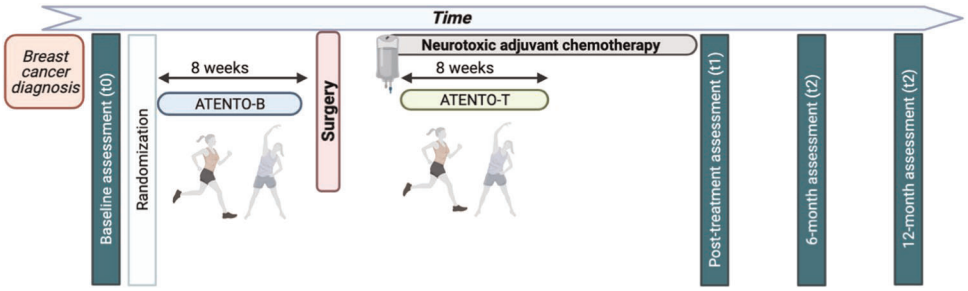

FIGURE 2 ATENTO program timings. Created with Biorender.com[Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 The ATENTO program components in detail

ATENTO progam Frequency: >2 days/week depending of recovery following ATOPE+ results					
		General phase		Specific phase	
Components		Time (min) or volume	Intensity	Time (min) or volume	Intensity
Aerobic (continuous and interval training)		20–30′	Low–moderate 30%–50% HRR (Luan et al., 2019)	10–20′	Moderate–high 40%–85% HRR (Luan et al., 2019)
Strength		8 All body exercises, 1–2 sets of 12–15 repetitions	Moderate 40%–70% RM (Luan et al., 2019)	8 Exercises, 3–4 sets of 6–10 repetitions	Moderate–high 50%–85% RM (Luan et al., 2019)
VAT	Myofascial exercises	10–15′	–	10–15′	–
	Breathing techniques	8–10′	–	10–15′	–

Abbreviations: HRR, heart rate reserve; RM, repetition maximum; VAT, vagal activation techniques.

an overall warm-up of 8–10 min (light intensity aerobic, joint mobility, and stretching exercises), the main part of 60 min with cardiovascular (10–30 min) and strength (30–50 min) exercises, and a final part of 20 min with VAT exercises aimed at promoting physical and mental recovery. Elliptical trainer, elastic bands, dumbbells, and mats will be required for the implementation of the program.

2.7 | Statistical analyses and sample size calculation

We will use the Statistical Package for the Social Science (IBM© SPSS© Statistic version 25 Corp.) considering significant results at $p \leq 0.05$. Analysis of data will be based on intention-to-treat and imputation methods will be used for missing data.

Characteristics of the participants at baseline will be described for the entire sample, and study groups (ATENTO-B and ATENTO-T). Continuous data will be summarized as mean and standard deviation ($m \pm SD$), while categorical variables will be summarized as number and percentage (n, %). The normality of the variables will be checked with the Kolmogorov–Smirnov test and visual reinforcement. A baseline comparison will be made to test homogeneity between two groups using the Student's t test or Mann–Whitney U as appropriate.

A generalized linear mixed model will be used to test the effect of the ATENTO program on QoL, central and peripheral neurotoxicity, and the remaining health outcomes, analyzing the time X group interaction for between- and within-group changes. All models will be adjusted for statistically significant baseline differences. The magnitude of change over time and differences by the group will be calculated using Cohen's d effect size values.

The sample size was calculated using the EORTC QLQ-C30 version 3.0 (Aronson et al., 1993) and calculations from the previous study to detect a mean difference in the global QoL subscale between the ATENTO-B and ATENTO-T groups of 14.6 (69.5 ± 18.0 vs. 54.9 ± 19.6; Steindorf et al., 2019). Assuming an α error of 0.05, a power of 85% and an effect size of 0.79 (based on the results of the reference study), we need a sample of 24 participants for each group (G*Power v. 3.1). Assuming a possible 15% dropout rate, based on a previous similar study (Mijwel et al., 2018) in which 14 participants dropped out after randomization and 10% dropped out during the intervention, we will recruit 28 participants per group (total $n = 56$).

3 | DISCUSSION

This study will target avoiding QoL reduction through the prevention of neurotoxicity. To this end, we will study the efficacy of ATENTO, a multimodal program based on TE and VAT, performed at two different time points: before and throughout adjuvant chemotherapy in women with newly diagnosed BC.

Early evidence suggests the implementation of prehabilitation programs in oncological patients is more powerful than rehabilitation interventions (Treanor et al., 2018). Exercise-based interventions have been demonstrated to be optimal in primary and secondary prevention in cancer patients (Bade et al., 2015). Improvements in QoL have also been observed with intervention programs before surgical and systemic treatments for cancer (Treanor et al., 2018). In addition to improving posttreatment outcomes, prehabilitation may be one way to maximize treatment effectiveness, recovery, and survival (Giles & Cummins, 2019). In addition, multimodal interventions before medical treatments appear to provide better treatment experiences than unimodal interventions (Santa Mina et al., 2017). Our study aims to determine whether an early multimodal program based on TE and VAT can prevent neurotoxicity and QoL reduction derived from medical treatment in women newly diagnosed with BC.

There are some limitations in this study. The short and variable period of time between cancer diagnosis and surgery, as well as the

psychological impact of diagnosis, could make adherence and completion of the program difficult for the ATENTO-B group. However, just 3–4 weeks of moderate-vigorous prehabilitation involving physical exercise has benefits for tumors in BC (Ligibel et al., 2019) and a review has shown that prehabilitation is feasible with good levels of adherence (Treanor et al., 2018). Also, we will control psychological status during the intervention program, and we will consider a minimum of 75% of adherence.

If ATENTO-B obtains better feasibility and efficacy results than ATENTO-T, similar programs should be piloted for the time interval between diagnosis and surgery. In addition, that window may be an excellent opportunity to provide care, prepare BC patients for medical treatment and survivorship, improve post-treatment outcomes, and reduce the use of health services. In contrast, if ATENTO-T results in better outcomes, it may be necessary to consolidate the protocols for the application of this type of multimodal program based on tailored TE and VAT in BC patients. In summary, our results may help to improve the protocols of multimodal programs that prevent and address treatment-related side effects such as neurotoxicity and to improve QoL in women newly diagnosed with BC.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This trial has been approved by the Committee of Biomedical Research Ethics of Andalucía (Granada, Spain) (0091-N-19) and it follows the principles of the Helsinki Declaration (2013 version) (World Medical Association, 2014). All participants will be informed verbally and in writing before signing the informed consent form. If any change that could substantially affect the implementation of the study (related to the planned objectives, design, or methods) is needed, it will be communicated to the Ethics Committee. The study will be carried out in accordance with the data protection law (3/2018).

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