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Research Paper

Exercise-based cardio-oncology rehabilitation for cardiotoxicity prevention during breast cancer chemotherapy: The ONCORE randomized controlled trial

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ABSTRACT

Background: Breast cancer (BC) treatment with anthracyclines and/or anti-human epidermal growth factor receptor-2 (HER2) antibodies is associated with an increased risk of cardiovascular disease complications, including cancer therapy-related cardiac dysfunction (CTRCD). While Cardio-Oncology Rehabilitation (CORe) programs including exercise have emerged to minimize these risks, its role in preventing CTRCD is unclear.
Objectives: We investigated the effectiveness of an exercise-based CORe program in preventing CTRCD [left ventricular ejection fraction (LVEF) drop ≥10% to a value <53% or a decrease >15% in global longitudinal strain (GLS)]. Secondary outcomes examined changes in cardiac biomarkers, physical performance including peak oxygen consumption, psychometric and lifestyle outcomes. Safety, adherence, and patient satisfaction were also assessed.
Methods: This is a randomized controlled trial including 122 early-stage BC women receiving anthracyclines and/or anti-HER2 antibodies, randomized to CORe ($n = 60$) or usual care with exercise recommendation ($n = 62$). Comprehensive assessments were performed at baseline and after cardiotoxic treatment completion. The average duration of the intervention was 5.8 months.
Results: No cases of CTRCD were identified during the study. LVEF decreased in both groups, but was significantly attenuated in the CORe group [−1.5% (−2.9, −0.1); $p = 0.006$], with no changes detected in GLS or cardiac

Abbreviations and acronyms: 30STS, 30-s sit-to-stand; 6MWT, Six-minute walk test; BC, Breast cancer; BMI, Body mass index; CORe, Cardio-oncology rehabilitation; CTRCD, Cancer therapy-related cardiac dysfunction; CVD, Cardiovascular disease; FACT-B, Functional assessment of cancer therapy—breast; GLS, Global longitudinal strain; GLTEQ, Godin Leisure Test Exercise Questionnaire; HADS, Hospital anxiety and depression scale; HER2, Human epidermal growth factor receptor-2; ITT, Intention-to-treat; LVEF, Left ventricular ejection fraction; NT-proBNP, N-terminal probrain natriuretic peptide; PA, Physical activity; PP, Per-protocol; PREDIMED, Prevención con dieta mediterránea; RCT, Randomized control trial; VO_{2peak}, Peak oxygen consumption.

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biomarkers. The CORe intervention led to significant body mass index (BMI) reduction ($p = 0.037$), especially in obese patients [3.1 kg/m^2 (1.3, 4.8)]. Physical performance and quality-of-life remained stable, while physical activity level increased in both groups. No adverse events were detected.

Conclusions: This study suggests that CORe programs are safe and may help attenuate LVEF decline in BC women receiving cardiotoxic therapy and reduce BMI in obese patients.

Introduction

Breast cancer (BC) affected 576.300 women and caused of 157.100 deaths in Europe in 2020.[1] Although survival has increased due to early diagnosis and advances in treatment, an increase in morbidity caused by the disease itself and the side effects of treatments has been reported.[2] Chemotherapy with anthracyclines and/or anti-human epidermal growth factor receptor-2 (HER2) antibodies has been shown to be effective against cancer cells in BC patients, but has been associated with an increased risk of cardiovascular disease (CVD).[3–5] The development of cancer therapy-related cardiac dysfunction (CTRCD) has a dynamic course throughout the disease.[6] Depending on the oncological treatment, the cumulative incidence can reach up to 20% if asymptomatic deterioration of left ventricular ejection fraction (LVEF) is considered, and up to 6% if symptoms of heart failure occur.[7]

The concept of CTRCD has evolved over time, with the most widely accepted proposal being a LVEF drop of ≥10% to an absolute value <53%.[8] In addition, a decrease in global longitudinal strain (GLS) of >15% from baseline has been considered a subclinical marker of LVEF in this setting.[8] Likewise, circulating biomarkers such as troponin-I and N-terminal probrain natriuretic peptide (NT-proBNP) have been included for a comprehensive assessment and monitoring of cardiac function.[9] In addition, cardiopulmonary function assessed by peak oxygen consumption (VO_{2peak}), is an integral measure of the circulatory, respiratory, and musculoskeletal systems,[10] which may be compromised during chemotherapy.[11] Recently, efforts have been made to harmonize the different definitions and classifications of CTRCD,[12] as well as the diagnostic, preventive and therapeutic management of patients, providing the first European clinical practice guidelines in cardio-oncology.[6]

Exercise prescription in cardio-oncology rehabilitation (CORe) programs is increasingly recognized as a complementary non-pharmacological cardioprotective tool.[13] It also aims to attenuate or improve physical performance, protect psychosocial status and improve patient's lifestyle.[13,14] The experience of multimodal cardiac rehabilitation programs in improving the prognosis of patients with various CVD may provide an opportunity to extend their potential benefits to BC patients at risk of cardiotoxicity.[14] However, while exercise has been shown to be safe and effective against many treatment side effects, its role in CTRCD prevention is uncertain.[15–18]

This paper presents the results of the ONCORE study, a randomized clinical trial designed to assess the effect of an exercise-based CORe intervention on CTRCD prevention in early-stage BC women receiving potentially cardiotoxic chemotherapy, compared with usual care with physical activity (PA) recommendations. Primary outcomes included changes in LVEF and/or left ventricular GLS as core markers of CTRCD between the exercise-based CORe intervention (CORe) and control groups. Secondary outcomes included the effect of the intervention on circulatory biomarkers, cardiopulmonary function assessed by VO_{2peak}, physical performance, psychometric and lifestyle outcomes.[10] The safety of the intervention, patient satisfaction and adherence to the CORe program were also assessed. It was hypothesized that (i) the exercise-based CORe program would be effective in preventing CTRCD in women with early-stage BC compared to usual care, and (ii) patients in the CORe group would maintain or improve their physical performance and psychosocial status.

Methods

Design and procedures

Details of the ONCORE trial protocol have been published previously.[19] Briefly, this prospective randomized control trial (RCT) compares the effectiveness of an exercise-based CORe program for the prevention of CTRCD in early-stage BC women receiving anthracyclines and/or anti-HER2 antibodies, as compared with usual care with PA recommendations. The study, based on collaboration between the cardio-onco-hematology, cardiac rehabilitation and oncology units of the University Clinical Hospital of Santiago de Compostela (Galicia, Spain), complies with the Declaration of Helsinki and was approved by the Clinical Research Ethics Committee of Galicia (code 2018/083). An amendment to the original protocol was approved in 2020 due to the outbreak of the COVID-19 pandemic, which was also approved by the Ethics Committee and duly recorded in the trial protocol (NCT03964142).

Participants

Women aged 18–70 years with a first diagnosis of stage I-III BC, who were planned to receive adjuvant or neoadjuvant anthracyclines and/or anti-HER2 antibodies, without contraindications to participate in an exercise-based CORe program, and providing informed written consent were eligible. Exclusion criteria included previous CVD and having received ≥20% of the planned cardiotoxic chemotherapy at enrollment.

Interventions

After baseline assessment, patients were randomly assigned to the CORe group or the usual care group by simple randomization (Fig. 1). The CORe group underwent a physiotherapist-supervised exercise program in the cardiac rehabilitation ward (one-hour session, two days/week, including strength training with body weight and elastic bands and aerobic exercise at 50–85% of heart rate reserve), during the period of chemotherapy treatment (between 3 and 12 months, depending on whether the treatment included anti-HER2 antibodies). During the COVID-19 pandemic (from March 2020 to March 2022), exercise sessions were conducted by videoconference. Further details of the standard session of both modalities are provided in Supplementary material online, Table S1 A. The usual care group received PA advice via telephone every two months with motivational interviewing by the physiotherapist until final assessment. All participants underwent the same monitoring at the cardio-onco-hematology unit every three months for cardiotoxicity detection (including echocardiography and cardiac biomarkers, as appropriate) and control of CVD risk factors.

Outcomes

Anthropometric characteristics, cardiovascular risk factors, and characteristics of the oncological process were assessed at baseline.

Primary and secondary variables were collected at baseline and two weeks after chemotherapy completion. Primary outcomes were the occurrence of cardiotoxicity defined as ≥10% decrease in LVEF to an absolute value of <53% and/or > 15% decrease in GLS from baseline[8] as measured by serial echocardiography, and record of clinical heart failure episodes. All echocardiographic studies were performed by the same

echo technician and measurements were reviewed by the same cardiac imaging specialist using the EchoPAC workstation (GE Healthcare US), both blinded to the intervention group. Secondary outcomes included 1) biomarkers (NT-proBNP and troponin-I), 2) anthropometric characteristics, 3) VO_{2peak} measured by cardiopulmonary exercise testing (baseline, $n = 79$; post-intervention, $n = 48$) or estimated by six-minute walk distance (6MWT) during the COVID-19 pandemic (baseline, $n = 41$; post-intervention, $n = 61$) by an equation obtained from a linear regression model combining the total meters walked in the 6MWT, age and weight; 4) lower limb strength calculated by the number of repetitions in the 30 sit-to-stand (STS) test and upper limb strength by handgrip dynamometry; 5) psychosocial and lifestyle aspects: Health-related quality of life using the Functional Assessment of Cancer Therapy—Breast (FACT-B)[20]; Hospital Anxiety and Depression Scale (HADS)[21]; level of PA quantified by the Godin Leisure Test Exercise Questionnaire (GLTEQ)[22]; and adherence to the Mediterranean diet using the PREDIMED (PREvención con DIeta MEDiterránea) questionnaire.[23]

Adherence to the exercise-based CORe program, safety of the intervention based on the occurrence of adverse events and participant satisfaction on a scale of 0–10 were also collected as exploratory variables.

Sample size calculation and statistical analysis

The sample size, calculated considering an expected prevalence of asymptomatic LVEF deterioration of 20%[7] in the usual care group and 10% in the CORe group using the Marrugat's et al.[24] formula, resulted in 154 participants in each group. Further details can be found in the study protocol document.[19]

For descriptive analyses, continuous variables were expressed as mean ± standard deviation and categorical variables were expressed as n (%). The distribution and normality of the variables were determined by one-sample Kolmogorov–Smirnov tests.

The primary analysis was performed using the intention-to-treat (ITT). Missing data during follow-up were completed using multiple imputation. Specifically, 1000 imputed datasets were created with this algorithm and the pooled results were analyzed according to Rubin's rules, which combine the estimates and standard errors. Continuous variables were compared between groups using ANCOVA analysis, considering the baseline value of each variable. Descriptive data for primary and secondary variables at baseline and post-intervention were

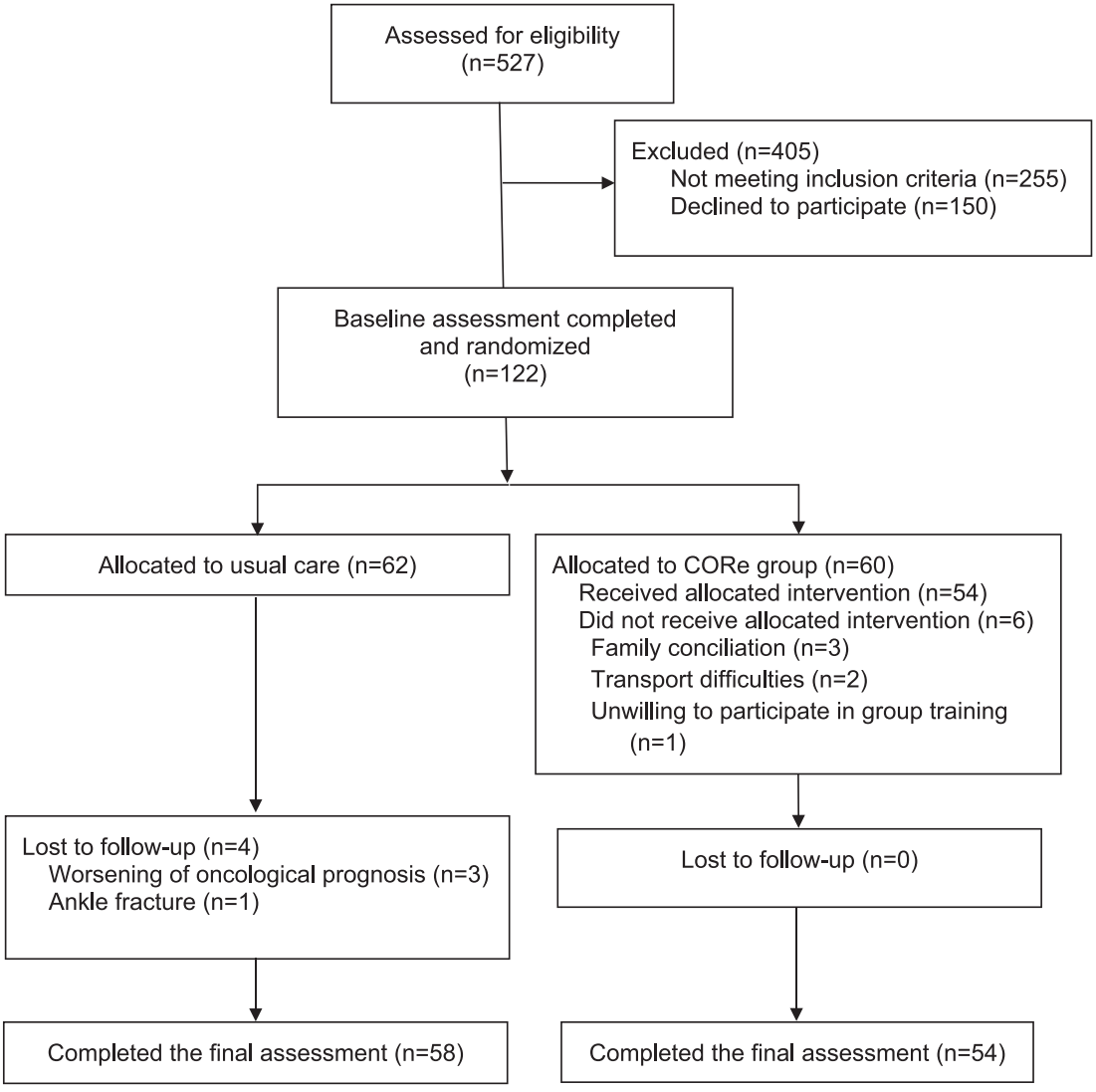

Fig. 1. CONSORT diagram of ONCORE study.
Caption: A total of 527 patients were screened for eligibility, of whom 122 were included and randomized to usual care ($n = 62$) or CORe groups ($n = 60$). After the intervention, lasted between 3 and 12 months depending on whether the treatment included anti-HER2 antibodies, 58 patients from usual care and 54 from CORe groups completed the final assessment.

expressed as marginal means and 95% confidence intervals. Such means were obtained based on linear additive models including baseline values and intervention effect.

In addition, the per-protocol (PP) analysis including all participants who completed the final post-intervention assessment is provided in Supplementary material online, Table S2. Results also include all significant changes between- and within- groups obtained in the PP analysis (in superscript). Independent *t*-tests or the Mann-Whitney *U* test were used to compare study outcomes between groups at baseline and post-intervention, as appropriate. Paired t-tests or the Mann-Whitney U test were used to examine intra-group changes over time. Two-sided $p < 0.05$ was considered statistically significant. Effect sizes were calculated using Cohen's d, with an insignificant effect <0.25; slight effect between 0.25 and 0.5; a moderate effect between 0.5 and 0.8; and a large effect >0.8. Analyses were performed using R and IBM SPSS.

Results

Participants

From August 2018 to March 2021, a total of 122 out of 527 eligible patients (23%) were included in the trial (Fig. 1). The study ended in March 2022, when the last enrolled participant completed the follow-up and final assessment. Sixty-two patients were assigned to the usual care group and 60 to the CORe group. Of these, 58 and 54 women, respectively, performed the final assessment and completed the study. The baseline characteristics of the participants are summarized in Table 1, with no differences between groups. The mean age of participants was 48.8 ± 8.2 years, and >60% were premenopausal. Mean body mass index (BMI) and abdominal circumference were slightly above recommended values, and hyperlipidemia was the predominant CVD risk factor (37.7%). Most participants received neoadjuvant chemotherapy (60.7%) and had BC at stage II (51.6%). The number of patients expressing HER2+ was similar in both groups. Most participants had received 0 cycles of anthracyclines or anti-HER2 at baseline (57.4%).

Primary outcomes

Resting echocardiographic measures, recorded at baseline and post-intervention, are summarized in Table 2. The ANCOVA reflected significant differences in post-intervention LVEF between groups ($p = 0.006$) (Graphical Abstract), with an effect size of 0.4 in favor of the CORe group, while GLS was unchanged ($p = 0.19$). Although mean values of LVEF and GLS decreased significantly over time in both groups, none of the participants met the criteria for cardiotoxicity (decrease in LVEF ≥10% from baseline and below 53% and/or decrease in GLS >15% from baseline). Of note, nine participants (usual care, $n = 6$; CORe, $n = 3$) showed a decrease in LVEF >10% from baseline during chemotherapy.

A post-hoc statistical power analysis including individuals from both groups ($n = 62$ and $n = 60$), an effect size of 0.4 for LVEF and a significance level of $\alpha = 0.05$ resulted in a power of 69% (G*Power version 3.0.10, Düsseldorf, Germany). In the PP analysis, similar results were observed for LVEF with an effect size of 0.7. For GLS, significant changes between groups were observed at post-intervention ($p = 0.024$) but also at baseline ($p > 0.05$), with higher values in the CORe group (Supplementary material online, Table S2).

Secondary outcomes

Changes in biomarkers, BMI, functional assessment and psychometrics are shown in Table 2. In the ITT analysis, only BMI showed significant changes between groups after the intervention ($p = 0.037$, effect size 0.3), with obese patients (BMI > 30) in the CORe group showing the greatest reduction (from 35.7 kg/m^2 [95% CI, 32.7–38.6] to 32.9 kg/m^2 [95% CI, 31.9–34]). The PP analysis showed significant between-group differences after intervention in VO_{2peak}, 30STS test and left handgrip strength ($p < 0.05$ for all analyses) in favor of the CORe group.

Both the ITT and PP analysis showed no changes in cardiac biomarkers and psychometric variables after the intervention. PA measured by the GLTEQ increased significantly in both groups, with no significant differences between them at follow-up.

Exploratory outcomes

Overall adherence [31.7 sessions attended (SD, 25.8) /48.6 prescribed sessions (SD, 37.6)] to the exercise-based CORe program was 67%. Twelve of 54 patients (23%) attended >80% of the prescribed

Table 1
Baseline characteristics of study participants.

Variables	All ($N = 122$)	Usual Care (n = 62)	CORe (n = 60)
	Mean (SD)/n (%) *		
Age, years	48.87 (8.24)	48.92 (8.51)	48.82 (8.02)
Heigh, cm	161.24 (5.73)	161.34 (6.16)	161.13 (5.31)
Weight, kg	69.01 (13.62)	69.77 (13.18)	68.23 (14.12)
BMI, kg/m^2	26.62 (5.52)	26.86 (5.31)	26.36 (5.77)
Waist perimeter, cm	89.17 (13.09)	90.26 (12.22)	88.05 (13.95)
Resting heart rate, bpm	77.91 (10.81)	77.94 (11.14)	77.88 (10.54)
Systolic blood pressure, mmHg	119.97 (16.12)	119.73 (16.54)	120.22 (15.82)
Diastolic blood pressure, mmHg	78.98 (9.87)	78.89 (9.71)	79.08 (10.11)
Menopausal status			
Premenopausal	77 (63%)	40 (65%)	37 (62%)
Postmenopausal	45 (37%)	22 (36%)	23 (38%)
Classic cardiovascular risk factors			
Arterial hypertension	11 (9%)	5 (8%)	6 (10%)
Hyperlipemia	46 (38%)	18 (29%)	28 (47%)
Diabetes	5 (4%)	2 (3%)	3 (5%)
Smoker	12 (10%)	9 (15%)	3 (5%)
Ex-smoker	47 (39%)	21 (34%)	26 (43%)
BC stage			
I	29 (24%)	9 (15%)	20 (33%)
II	63 (52%)	37 (60%)	26 (43%)
III	30 (25%)	16 (26%)	14 (23%)
Molecular subtype			
Luminal A	30 (25%)	18 (29%)	12 (20%)
Luminal B HER2-	33 (27%)	12 (19%)	21 (35%)
Luminal B HER2+	31 (25%)	18 (29%)	13 (22%)
Pure HER2	10 (8%)	4 (7%)	6 (10%)
Triple-negative	17 (14%)	9 (15%)	8 (13%)
Chemotherapy			
Neoadjuvant	74 (61%)	35 (57%)	39 (65%)
Adjuvant	48 (39%)	27 (44%)	21 (35%)
Affected breast			
Right	55 (45%)	23 (37%)	32 (53%)
Left	63 (52%)	38 (61%)	25 (42%)
Bilateral	4 (3%)	1 (2%)	3 (5%)
Cycles of anthracyclines or AntiHER2 received at baseline assessment			
0 cycles	70 (57%)	36 (58%)	34 (57%)
1 cycle	44 (36%)	21 (34%)	23 (38%)
2 cycles	8 (7%)	5 (8%)	3 (5%)

* Continuous variables are presented as mean (SD, standard deviation) and categorical variables are presented as n (%).

Table 2
Primary and secondary outcomes differences between groups at post-intervention (intention-to-treat analysis).

Measure	Usual Care (n = 62) Mean (CI 95%)		CORe (n = 60) Mean (CI 95%)		MSD between group changes (CI 95%)	ANCOVA *P*-value
	Baseline	Post-intervention	Baseline	Post-intervention		
Primary outcomes						
LVEF, %	65.4 (64.4, 66.4)	62.7 (61.8, 63.7)[a]	66.3 (65.2, 67.4)[a]	64.2 (63.2, 65.2)	−1.5(−2.9, −0.1)	**0.006**[b]
GLS, %[c]	−20.5 (−20, −20.9)	−19.9 (−19.3, −20.4)[a]	−21.4 (−20.9, −22)[a]	−20.4 (−19.9, −21)	−0.5(−1.3, 0.3)	0.193[b]
Secondary Outcomes						
Circulating Biomarkers						
NT-proBNP, pg/ml	81.5 (47.1119.9)	57.6 (45.4, 69.9)	70.3 (50.6,89.9)	58.1 (45.7, 70.6)	−0.5(−18.1, 17.1)	0.901
Troponin I, ng/ml	0.0180 (0.0168, 0.0192)	0.0171 (0.0168, 0.0175)	0.0178 (0.0161, 0.0196)	0.0172 (0.0169, 0.0175)	−0.0001 (−0.0005, 0.0004)	0.891
Anthropometrics						
BMI, kg/m^2	26.8 (25.5, 28.2)	27.4 (26.7, 28.1)	26.3 (24.8, 27.8)	26.2 (25.5, 27)	1.1 (0.1, 2.1)	**0.037**
BMI <18, kg/m^2	18.1 (16, 20.2)	19.4 (18.1, 20.7)	-	20.3 (19.0, 21.5)	0.9 (−0.9, 2.7)	
BMI 18–25, kg/m^2	22.8 (22, 23.6)	25.9 (25.1, 26.6)	22.3 (21.7, 22.8)	25.1 (24.4, 25.8)	0.7 (−0.3, 1.8)	
BMI 25–30, kg/m^2	26.8 (26.3, 27.4)	30.5 (29.7, 31.3)	27.8 (27.1, 28.4)	28.6 (27.7, 29.4)	1.9 (0.8, 3.0)	
BMI >30, kg/m^2	34.1 (31.9, 36.2)	35.1 (33.8, 36.3)	35.7 (32.7, 38.6)	32.0 (30.7, 33.3)	3.1 (1.3, 4.8)	
Functional assessment						
VO2peak, ml/kg/min	20.6 (19.7, 21.6)	20.2 (19.4, 20.9)	21.3 (20.3, 22.3)	20.9 (20.2, 21.7)	−0.8 (−1.9,0.3)	0.173[b]
30STS, reps	19.5 (18.5, 20.6)	20.1 (19.2, 21.1)	20.5 (19.4, 21.7)	21.6 (20.6, 22.5)[a]	−1.4 (−2.7, 0.1)	0.101[b]
Right handgrip, kg	25.1 (24, 26.2)	24.7 (23.8, 25.6)	25.3 (24.2, 26.5)	25.0 (24.1, 25.9)	−0.3 (−1.6, 1.0)	0.802
Left handgrip, kg	23.5 (22.2, 24.7)	22.5 (21.5, 23.4)[a]	24.6 (23.4, 25.8)	23.7 (22.7, 24.6)	−1.2 (−2.5, 0.2)	0.131[b]
Psychosocial and lifestyle aspects						
FACT-B	101.8 (97.2, 106.3)	103.3 (99.4, 107.3)	104.5 (100.5, 108.5)	101.4 (97.3, 105.4)	2.0 (−3.7,7.7)	0.762
HADS, depression	3.9 (3.1, 4.7)	4.0 (3.3, 4.7)	4 (3.2, 4.8)	4.1 (3.4, 4.9	−0.1 (−1.2, 0.9)	0.783
HADS, anxiety	7.1 (6, 8.1)	6.2 (5.4, 7.1)[a]	6.6 (5.8, 7.4)	6.1 (5.3, 7)	0.1 (−1.1, 1.3)	0.974
PREDIMED[c]	8.3 (7.7, 8.8)	9.6 (9.1, 10.1)[a]	9.1 (8.5, 9.6)	9.7 (9.2, 10.2)	−0.1 (−0.9, 0.7)	0.700
GLTEQ	17.9 (15.2, 20.5)	28.8 (25.8, 31.8)[a]	20.5 (17.3, 23.7)	25.2 (22.1, 28.2)[a]	3.6 (−0.8, 7.9)	0.069

Descriptive data at baseline were obtained using the available sample and post-intervention using multiple imputation.
Abbreviations: 30STS, 30-s sit-to-stand; BMI, body mass index; CORe, Cardio-Oncology Rehabilitation; CI, Confidence Intervals; FACT-B, functional assessment of cancer therapy—breast; GLTEQ, Godin Leisure Test Exercise Questionnaire; GLS, global longitudinal strain; HADS, hospital anxiety and depression scale; LVEF, left ventricular ejection fraction; MSD, Minimal Significant Difference; NT- proBNP, N-terminal brain natriuretic propeptide; PREDIMED, PREvención con DIeta MEDiterránea; VO2peak, peak oxygen uptake.
[a] Significant differences ($p \leq 0.05$) within groups in per-protocol analysis.
[b] Significant differences ($p \leq 0.05$) between groups in per-protocol analysis.
[c] Significant differences between the groups were observed at baseline ($p \leq 0.05$).

sessions; 26 patients (48%) attended between 60 and 80%, and 15 patients (28%) attended <60%. Of note, 12 HER2+ patients underwent BC surgery during the program and were unable to attend the sessions on the post-operative days, which were recorded as medical absences. The average duration of the exercise intervention was 5.79 months (95% CI, 4.42–7.17), with a wide range depending on whether anti-HER 2 agents were prescribed. The median duration was 13.2 months (95% CI, 11.5, 15) in HER2+ patients and three months (95% CI, 2.5, 3.2) for HER2- patients. Satisfaction with the CORe program was rated at 9.4 points (95% CI, 9.1, 9.6) on a scale of 0–10. There were no significant differences in the follow-up considering the time from initial to final assessment between control [7.8 months (5.6)] and intervention [7.4 months (5.7)] groups.

No adverse events occurred during the exercise sessions. There were no major adverse CVD events occurring in either group during the study, and only one case of pericardial effusion was observed in each group.

Discussion

In this randomized controlled trial testing an exercise-based CORe program in women with early BC treated with anthracyclines and/or anti-HER2 antibodies, it was hypothesized that the intervention would prevent cardiotoxicity defined as a ≥ 10% decrease in LVEF to a value <53% and/or a > 15% decrease in GLS,[8] compared with usual care. Although both groups experienced a decline in LVEF and GLS after chemotherapy, none of the study participants had CTRCD according to this definition, nor according to the European cardio-oncology guidelines.[6] Of note, the decline in LVEF was significantly attenuated in the CORe group ($p = 0006$), while there was no effect of the intervention on GLS. In addition, the CORe program was associated with a reduction in BMI in obese patients.

These findings show that an integrated cardiac rehabilitation strategy significantly attenuates the decline in LVEF in women with BC undergoing cardiotoxic treatment. Considering the pivotal prognostic significance of LVEF and its substantial contribution to the risk of cardiotoxicity in its broadest concept,[6,8] our results serve to emphasize the importance of incorporating exercise-based cardiac rehabilitation in the comprehensive management of BC patients treated with anthracyclines and/or anti-HER2 antibodies.

Parameters defining cancer therapy-related cardiac dysfunction

Previous research has examined the relationship between exercise and cardiac function assessed by resting echocardiography in BC patients undergoing chemotherapy, with various results. Consistent with our findings, the pilot RCT study by Hojan et al.[25] ($n = 46$) found significant differences in LVEF decline, but not in GLS, after a 9-week aerobic and strength training program in BC patients receiving trastuzumab. On the other hand, the systematic review by Murray et al.[15] found no significant changes in LVEF or GLS in women receiving cardiotoxic treatment after a 10-week exercise program. Also, neither the trial by Antunes et al.[18] ($n = 93$) nor the BREXIT study[26] ($n = 104$) testing a 5–6-month and a 12-month exercise program in women receiving anthracyclines, found a significant effect of exercise on resting LVEF and GLS, but a decreasing trend was observed in both groups. These findings are consistent with those of the TITAN trial,[27] ($n = 74$) which reported no significant changes in LVEF and GLS determined by cardiac magnetic resonance imaging, and a mildly decreased LVEF in the

overall cohort after a 13-month CORe program in women with BC receiving anthracyclines and/or anti-HER2 treatment.

These discrepancies could potentially be attributed to different cardiotoxicity risks based on treatment protocols and timing, along with disparities in the intensity and volume of exercise. For example, patients who receive anthracyclines alone show less impaired cardiac function than those who receive anthracyclines plus anti-HER2 antibodies.[28] It is possible that different patients require different exercise volumes to show beneficial changes in cardiac function assessed by resting echocardiography, as it has been described in patients with HF.[29] Further studies are needed to tailor the volume of exercise to the timing of the oncological process[30] and the cancer treatment regimen, aiming for the lowest safe but clinically relevant dose.[31]

Strikingly, in our study, no changes in circulating biomarkers considered promising predictors of CTRCD, including NT-proBNP and troponin-I, [27] were detected either from baseline or between groups after treatment.[32] These results align with previous investigations[17,18,27] that also found no effect of exercise on these markers. However, in the BREXIT study[26] troponin-I increased less in the exercise group than in the control group after chemotherapy, while no changes in BNP were found.[28]

Anthropometric characteristics

A noteworthy finding of our study was the interaction of the exercise-based CORe program with BMI ($p = 0.037$) in obese patients, which resulted in reduced BMI in this subgroup. In contrast, a systematic review and meta-analysis[33] including 14 RCTs reported no changes in weight and BMI after an exercise program in BC patients. However, a RCT by Irwin et al.[34] using dual-energy x-ray absorptiometry to assess body composition found an increase in lean mass and a decrease in fat mass six months after an aerobic exercise program in postmenopausal BC survivors. Therefore, even if there was an apparent beneficial effect of the intervention on BMI, a full assessment of body composition would be needed.

Physical performance

In our study, VO_{2peak} remained unchanged over time in both groups, although the PP analysis showed significantly better results in the CORe group. Given that chemotherapy can potentially reduce functional capacity as measured by VO_{2peak},[11] this preservation is particularly notable. Importantly, participants in both groups showed a significant increase in their physical activity levels from baseline, suggesting that even small interventions (such as PA counselling and regular follow-up) could have positive effects in this regard.

Similar to our findings, previous studies have also reported no changes in VO_{2peak} in BC patients assessed by cycle-ergometer cardiopulmonary exercise testing after different training programs, such as the RCT by Travier et al. ($n = 204$) that performed a 16-week aerobic and resistance exercise program during adjuvant chemotherapy,[35] or the single-group study by Haykowsky et al. ($n = 17$) that tested an aerobic exercise program during the first four months of adjuvant trastuzumab.[36] Conversely, other studies have reported significant increases in VO_{2peak} after an exercise program conducted during anthracycline treatment,[26,37,38] or after a 3-month exercise program during trastuzumab treatment.[39] These discrepancies, reported in various reviews and meta-analyses,[15–17] may be due to great heterogeneity in exercise prescription, adherence to the program, timing of cancer treatment,[30,40] or exercise performed in the control group.

For leg strength measured by the 30STS test, there was a significant increase in the number of repetitions performed in the CORe group over time; however, the superiority of the CORe group at follow up was only maintained in the PP analysis. While the RCT by Lee et al.[41] (n = 204) reported no changes in the 30STS test after eight weeks of high-intensity interval training, the prospective cohort study by Roldán et al.[42] ($n = 119$) found significant differences after an aerobic and strength exercise program in BC survivors. These variations may be due to a different specificity and intensity of the exercise.

For upper limb strength assessed by handgrip dynamometry, only the PP analysis showed differences between groups on the left side, with higher values in the CORe participants. However, this may be related to a significant decrease in left-side strength in the usual care group, where the left breast was predominantly affected (61.3%). In addition to strength, it is known that other limiting factors such as hypervigilance and central sensitization are limiting factors in BC arm function.[43] To properly compare upper limb strength in BC patients, a sample with similar timing and type of surgery would be required; however, this was out of the scope of the ONCORE study, which included patients with different surgery or no surgery.

Psychometric and lifestyle parameters

Quality of life measured by the FACT-B, and anxiety-depression assessed by the HADS, remained unchanged in both groups. Overall, anxiety scores were higher than depression scores, which may be due to diagnosis-related stress. Although the benefits of exercise on emotional well-being are well established,[44] previous similar studies have failed to show improvements in FACT-B[37] or HADS[35] scores. Nevertheless, maintaining baseline scores in a process that tends to worsen emotional health could be considered the minimum goal.

In terms of lifestyle, there were no differences between the groups in dietary patterns (PREDIMED) or PA levels (GLTEQ). However, both groups significantly increased their physical activity levels at follow-up. This could be explained by the intensified PA counselling with regular reminders provided to the usual care group: for ethical reasons, the telephone follow-up included individualized PA recommendations and goal setting, which may have attenuated the differences between the groups.

Safety, adherence and satisfaction with the core program

The CORe program was safe, with no adverse events occurring during the study period, as reported in other studies.[39,45] Adherence to the training sessions reached almost 70%, a rate that can be considered satisfactory given the duration of the intervention, which exceeded ten months in some HER2+ cases. Finally, the program was well accepted by the participants, who rated their satisfaction above 9/10 points, in line with previous pilot experiences.[46]

Study limitations

The ONCORE trial is, to our knowledge, the largest RCT investigating the role of exercise-based CORe programs in the prevention of CTRCD in patients with BC. It was designed to provide relevant and useful evidence for healthcare professionals, policy makers and patients, with the goal of improving patient outcomes in real-world settings. The multidisciplinary team involved in the design and conduct of the study ensured a comprehensive assessment of the patients, considering physiological and psychosocial aspects as well as patient experience throughout the trial.

However, we recognize several limitations. Firstly, no cases of CTRCD were detected according to the formal definition utilized in the study design. Recent data have indicated a lower incidence of cardiotoxicity within the studied population than it was expected at the time of trial design.[7] Consequently, although this trial could not prove the efficacy of the exercise-based CORe program in preventing CTRCD as previously defined, it is worth highlighting that it enrolled the largest number of participants in a CORe program to date and provided encouraging data suggesting attenuation of LVEF decline. Secondly, there was a limitation in terms of long-term cardiotoxicity monitoring, as evidence indicates that CTRCD can manifest months or even years

after treatment completion.[47] Lastly, due to pandemic-related safety recommendations concerning COVID-19, some VO_{2peak} measurements had to be estimated using the 6MWT. Despite these limitations, the ONCORE trial offers valuable insights into this area of knowledge and highlights the need for further research in order to enhance our understanding and refine clinical approaches.

Conclusions

In conclusion, the results of this RCT suggest that participation in an exercise-based CORe program may help attenuate the decline in LVEF associated with anthracyclines and/or HER2 antibody treatment among women with early-stage breast cancer, even in the absence of meeting formal criteria for CTRCD during the study period. Additionally, the intervention led to a significant weight reduction among obese patients. The program did not affect functional capacity and psychosocial status, and physical activity levels increased in both groups. Given their safety, exercise-based CORe programs can be considered as a valuable adjunctive therapy within the standard care of these patients. Further research is needed to validate and extend these findings to identify the most effective intervention and optimize its implementation.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pcad.2024.02.002.

Informed consent

All participants provided informed consent.

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CRediT authorship contribution statement

Estíbaliz Díaz-Balboa: Supervision. **Carlos Peña-Gil:** Supervision. **Beatriz Rodríguez-Romero:** Supervision. **Antonio I. Cuesta-Vargas:** Supervision. **Oscar Lado-Baleato:** Supervision. **Amparo Martínez-Monzonís:** Supervision. **Milagros Pedreira-Pérez:** Supervision. **Patricia Palacios-Ozores:** Supervision. **Rafael López-López:** Supervision. **José R. González-Juanatey:** Supervision. **Violeta González-Salvado:** Supervision.

Declaration of competing interest

The authors have declared that they have no relationships relevant to the contents of this paper to disclose.

Data availability

Data are available upon reasonable request.

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