Exercise to Prevent Anthracycline-Based Cardiotoxicity (EXACT): A Feasibility Study

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ABSTRACT

This study aimed to determine the feasibility and potential efficacy of a 12-wk aerobic exercise intervention to mitigate cardiotoxicity in those with breast and hematological cancer receiving anthracycline (AC) treatment. Individuals with breast or hematological cancer that were within 8 wk of initiating AC treatment attended a 12-wk biweekly exercise program. Participants performed aerobic exercise (35%–85% heart rate reserve) on treadmills for 20–45 min per session under the supervision of research staff. Feasibility was evaluated through participant accrual and retention, program adherence, and safety. Aerobic fitness, physical activity, quality of life, and fatigue were assessed along with AC-related serum cytokines (interleukin-1β, interleukin-6, tumor necrosis factor-α, and VEGF) to explore intervention efficacy. Over 12 months, 169 participants (115 breast cancer, 54 hematological) were screened for eligibility. Forty-nine were eligible (28 breast and 21 hematological) and 15 consented (31% accrual). Ten participants completed the study and five withdrew (67% retention). Average exercise session adherence was 73% with no exercise-related adverse events. Cardiopulmonary fitness, physical activity levels, quality of life, fatigue, and serum cytokines did not change over the course of the intervention. Participant accrual and retention, program adherence, and safety statistics in this trial were within the range of similar exercise trials involving individuals with cancer. Study findings showed no postintervention change in measures of quality of life, aerobic fitness, and inflammatory cytokines, suggesting that exercise may mitigate detrimental changes in these parameters while on AC. Overall, the exercise program was feasible, and the results warrant further investigation using a randomized controlled trial approach to investigate whether aerobic exercise therapy can mitigate cardiotoxicity and improve related health and fitness outcomes for individuals receiving AC treatment.

INTRODUCTION

Anthracyclines (ACs) are a class of chemotherapeutic medications commonly used to treat types of solid and blood-borne cancers. Although an effective antineoplastic therapy, AC treatment is also associated with cardiotoxic side effects, increased fatigue, and reduced quality of life (1). The incidence of cardiotoxicity from ACs is largely dose dependent and can occur several years after treatment completion (1,2). Cardiotoxicity from AC treatment typically manifests as left ventricular dysfunction, ranging from asymptomatic to congestive heart failure (1,3). The mechanisms of AC-mediated cardiotoxicity relate to myocardial cell death and dysfunction through reactive oxygen species production, p53 activation, and topoisomerase Ili’s inhibition (4). One downstream effect of AC-mediated cell death is thought to activate toll-like receptors that lead to depressed cardiac gene handling and increased levels of biological inflammatory markers (i.e., biomarkers) in surrounding cells, such as interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α [4]). Indeed, systemic levels of the inflammatory marker/mediator IL-6 can increase acutely after AC treatment and have been associated with left ventricular dysfunction (5,6). Elevated levels of other biomarkers observed during treatment (e.g., vascular endothelial growth factor [VEGF]) have also been associated with reduced quality of life and fatigue (7).

Current management strategies to combat AC-mediated cardiotoxicity include pharmacological therapies to treat heart failure (i.e., neurohormonal blockade) or the use of cardioprotective medications, such as dexrazoxane (8). Although these medications can be used to limit toxicity during treatment, they are unlikely to address the numerous other factors that increase the risk of AC-mediated cardiotoxicity over the long term, such as hypertension, diabetes, dyslipidemia, and other cardiovascular disease risk factors (9). Notably, the prevalence of these risk factors has been shown to be higher in cancer survivors in...
comparison with cancer-free siblings (e.g., hypertension 40% vs 26%) (9). These risk factors have also been shown to significantly increase the risk of cardiotoxicity. For example, developing hypertension after cancer treatment has been demonstrated to increase cardiotoxic risk by a factor of 12 (9). Thus, there is a need to develop adjunct therapies to better prevent/manage AC-related cardiotoxicity. An approach that has substantial preclinical evidence supporting its use in combating several facets of AC cardiotoxicity is exercise (10).

The role of exercise in improving cardiovascular function has been well documented (11), yet only in recent years has it garnered attention as a potential nonpharmacologic cardioprotective therapy for individuals receiving ACs and other known cardiotoxic therapies (12). Preclinical studies have demonstrated that aerobic exercise therapy (AET) performed before, during, or after treatment can reduce or prevent cardiotoxicity (10,12,13). As previously noted, the generation of reactive oxygen species and the effects thereof remain putative causes for AC-mediated cardiotoxicity, in part by inducing mitochondrial dysfunction and myocardial cell death. Notably, AET has been shown to reduce overall reactive oxygen species production, improve resistance to reactive oxygen species, and mitigate mitochondrial damage and myocardial cell death in rodent models (14–16). Thus, AET may help lessen dysfunction at the cellular level of the heart, thus helping to maintain cardiac function. Evidence also suggests that AET improves the clearance of ACs from the myocardium, thereby potentially mitigating cardiac damage (17). Importantly, AET has also been shown to preserve cardiac function during AC administration in rodent models (17). Although evidence from numerous animal studies has shown AET to be a promising strategy to attenuate AC-induced cardiotoxicity, few human clinical trials have been conducted.

One clinical trial investigated the effect of exercise 24 h before AC administration, finding that 30 min of aerobic exercise reduced the risk of a cardiotoxic biomarkers and improved systolic function (18). Baseline exercise testing has also been able to predict changes in functional capacity with AC treatment (19). However, this does not answer the question of whether regular AET (e.g., twice per week) during treatment can attenuate cardiotoxicity. Although several recent and ongoing trials are investigating AET to prevent AC-mediated cardiotoxicity, including CREATE (ClinicalTrials.gov: NCT03131024 [20]), TITAN (ClinicalTrials.gov: NCT01621659), and two others (ClinicalTrials.gov: NCT02454777 [21,22]; ISRCTN registry: 32617901 [23]), no results have been published. Although human trials are ongoing, cancer survivors and healthcare professionals continue to question whether it is feasible and safe for individuals with cancer receiving a known cardiotoxic therapy to exercise during treatment. Accordingly, the purpose of this study was to determine the feasibility and potential efficacy of a 12-wk AET intervention to mitigate cardiotoxicity in individuals with breast or hematological cancer receiving AC treatment. Specific objectives of this trial were to determine accrual rate (i.e., recruitment), program adherence, retention, and safety.

**METHODS**

**Design and Procedures**

The protocol has been previously described (24). In brief, exercise to prevent anthracycline-based cardiotoxicity (EXACT) was a single-arm (pre- and post-test) feasibility study of a supervised progressive AET intervention for individuals with breast and hematological cancer receiving AC therapy. The study was approved by the Nova Scotia Health Authority Research Ethics Board (REB File no. 1019999; Halifax, NS) and was registered at ClinicalTrials.gov (NCT02471053).

**Participants**

Individuals with breast and hematological cancer were recruited through local oncology clinics. Participants were included if they were within 8 wk of receiving their first dose of ACs, scheduled to receive a minimum dose of 100 mg·m⁻² doxorubicin, 150 mg·m⁻² epirubicin, or 120 mg·m⁻² daunorubicin, were between 18 and 70 yr of age, and were cleared by their medical oncologist/hematologist to participate in the study. Participants were excluded if they had previous cancer diagnosis, current cardiovascular or cognitive comorbidities, known absolute exercise contraindications as defined by the American College of Sports Medicine (25), or metastatic disease.

**Exercise Intervention**

Participants were asked to complete two supervised exercise sessions per week for 12 wk. Individuals completed a nonlinear exercise intervention on a treadmill, which has previously been described (24). The framework for exercise prescription in oncology research, which is based on principles of exercise physiology, individualization, specificity, and progressive overload to optimize safety and efficacy, was used to design the exercise intervention (26). In brief, the intervention was designed with periods of progressive overload and built-in rest periods to minimize fatigue and/or injury. Session durations ranged from 20 to 45 min, and session intensity was typically inversely proportional to volume. Target heart rates were determined based on the participant’s resting and peak heart rates from a baseline cardiopulmonary exercise test (CPET). Session intensities ranged from 35% to 83% heart rate reserve (calculated as heart rate reserve = resting heart rate + [peak heart rate – resting heart rate] × [intensity quotient]). Heart rate was monitored during each session using a Polar A360 HR monitor (Polar Electro Canada Inc., QC, Canada). Participants engaged in a 5-min warm-up and finished with a 10-min cooldown to normalize heart rate at the end of each session. All exercise sessions were supervised by a Canadian Society for Exercise Physiology Certified Personal Trainer. Exercise sessions were scheduled to best accommodate participants’ schedules; thus, not all participants exercised at the same time of day. Participants were encouraged not to attend exercise sessions if they experienced signs or symptoms that would not allow them to exercise safely (e.g., palmoplantar dysesthesia).

**Primary Outcomes**

The primary feasibility outcomes included participant accrual (i.e., recruitment), program adherence, retention, and safety. Participant accrual rate was defined as the number of participants who consented divided by the number deemed eligible to participate by their primary care oncologist/hematologist. Adherence was calculated by counting the total number of sessions attended by the participants divided by the total number of recommended sessions. Retention was determined by reporting the number of participants who completed baseline and postintervention testing. Safety was assessed weekly by monitoring the number of adverse events during the duration of the study.
Secondary Outcomes

Secondary outcomes included aerobic fitness, body weight, body mass index (BMI), waist circumference, cardiovascular function (resting heart rate and blood pressure), serum cytokines, self-reported physical activity levels, fatigue, and quality of life. A CPET was chosen from a General Electric Case V6.61 system (i.e., Bruce or Ramp treadmill protocol) to measure the estimated peak aerobic fitness (VO₂ [ml·kg⁻¹·min⁻¹]) and to record peak heart rate to calculate exercise intensities. Participants were given the most appropriate test by the research team cardiologist based on their medical history and perceived level of fitness. Each test was performed in accordance with the American Heart Association’s stress test guidelines (27). The stress test also enabled screening of participants to ensure they did not have exercise-induced contraindications (e.g., angina). Electrocardiographic recordings were taken before, during, and after CPET for further analysis. A cardiologist reviewed the patient’s CPET results to ensure there were no undiagnosed cardiovascular morbidities. Blood pressure was recorded via an automated cuff before, during, and after the CPET. Resting values were recorded for analysis.

Before the CPET, a blood draw of approximately 200 μL (finger-prick) was collected to measure blood-borne biomarkers. Samples were transported back to a laboratory and centrifuged at 9391g for 15 min to isolate serum. Samples were then stored at −20°C until analysis. Based on their potential mechanistic relevance to AC-mediated cardiotoxicity, the serum levels of IL-1β, IL-6, and TNF-α and VEGF (28–31) were quantified using a cytokine immunoassay via Bio-Rad’s MAGPIX Suspension Array System as per the manufacturer’s instructions.

Patient-reported measures of disease-specific fatigue and quality of life were measured using the Functional Assessment of Cancer Tools (FACT), which included FACT-G (general measures), FACT-Lym (lymphoma specific), or FACT-B (breast cancer specific), as appropriate, and the Functional Assessment of Chronic Illness Therapy—Fatigue (FACT-F). These valid and reliable tools for cancer populations are commonly used to assess cancer- and therapy-specific changes in quality of life (32–35).

Physical activity levels were assessed and calculated using the long form of the International Physical Activity Questionnaire (IPAQ [36]). It asks individuals to quantify the amount of time within the last week they performed physical activity at vigorous, moderate, and walking intensities during their occupation, transportation, home life, and leisure time in bouts of at least 10 min. Estimates of total activity were calculated by multiplying the amount of days the participant spent exercising by the amount activity minutes per day and by the estimated metabolic equivalent (MET) of the activity’s intensity (36). The product of this calculation gives a value in MET-minutes. Categorical physical activity levels were analyzed as either met activity guidelines (i.e., ≥600 MET-min·wk⁻¹) or did not meet guidelines (<600 MET-min·wk⁻¹ [37]).

Data Analysis

Participants who completed both pre- and posttesting (n = 10) were included in the final analyses. Participant demographic and study feasibility data were descriptively analyzed using frequencies for categorical data and mean and SD values for continuous variables. Analyses of preliminary efficacy variables, including estimates of change in total physical activity, BMI, aerobic fitness, resting and peak heart rates and blood pressures, rate pressure products, blood-borne biomarkers, and quality of life, were assessed using paired t-tests for normally distributed data. Data that were not normally distributed were evaluated using a Wilcoxon signed rank test and stated as such. The level of significance (α) was set at 0.05, and effect sizes were calculated using Cohen’s d (38). Analyses were conducted using IBM SPSS statistics 24 and Microsoft Excel 2019.

RESULTS

Primary Outcomes

Participants were recruited between March 2016 and August 2017 from Halifax, NS, and surrounding areas. Participant flow, accrual, and retention are shown in Figure 1. Of the 169 participants screened, 29% (n = 49) met the eligibility criteria (Fig. 2). This represents 24% of the individuals with breast cancer and 39% of the individuals with hematological cancer. The most common reasons for exclusion were not being within 8 wk of starting treatment (46% of total excluded) or being above the age cutoff (45% of total excluded). Of the 49 participants that were eligible to participate, only 32 were approached by research staff as the other 19 lived a significant distance outside of city (i.e., 1.5–2 h drive away). Thus, traveling twice per week to attend exercise sessions was deemed not feasible. Of the 32 participants that were approached, 47% (n = 15) consented and were accrued to the study. Eleven of the 17 that did not consent declined because of travel distance or perceived inconvenience.

Five of the 15 consenting participants withdrew before completion of the study resulting in a 33% study attrition rate. One participant withdrew before baseline testing and four withdrew shortly after baseline testing. Two of these four participants withdrew as a result of travel inconvenience, one for job-related reasons, and the final participant completed the full 12-wk intervention but was unable to attend follow-up testing. The final sample consisted of seven females (all breast cancer) and three males (all hematological). Participant characteristics are presented in Table 1.

Participants began the exercise intervention on average approximately 60 d after starting treatment (range = 2.7 to 18 wk; Table 1). Of note, all participants were consented within 8 wk of starting treatment; however, on average, it took 2–3 wk to schedule the baseline stress test. As a result, four participants were past the 8-wk window because treatment began when they started the AET. Session adherence ranged from 8% to 100% with an average of 72.9% ± 30.0%. One participant attended the baseline and postintervention testing but only completed the first week of the exercise intervention because of cancer/treatment-related fatigue. When this participant was removed from the data set, the average session adherence improved to 80.0% ± 20.0% (range 54%–100% of sessions).

Over the course of the study, no adverse events related to the AET intervention occurred. However, all participants reported experiencing treatment-related fatigue. In fact, fatigue was one of the primary reasons reported in personal correspondence for missing scheduled exercise sessions. Of note, during the exercise sessions, participants performed the prescribed exercise despite their elevated levels of fatigue.

Secondary Outcomes

Weight, BMI, and waist circumference did not change over the 12-wk intervention (Table 1). All parameters except for...
Peak heart rate during the CPET remained unchanged after the intervention. All but one (89%) of the participants with complete data were considered to have met the physical activity guidelines according to the IPAQ at enrolment, with 100% meeting guidelines after the 12-wk intervention. No differences before and after physical activity were found. A single participant reported that their job-related PA went from 4236 MET-min at baseline to 0 at postintervention time point. Notably, aerobic fitness remained unchanged as measured by peak estimated VO2 achieved during the CPET (33.6 ± 3.2

*Figure 1: EXACT study numerical values for recruitment and the exercise intervention for individuals with breast or hematological cancer.*
were found at the group level, varied responses in AET were
MET (3.5 mL·kg⁻¹·min⁻¹; other therapy-related fatigue (FACT-F)
i llness (FACT-Band-Lym), or therapy-related fatigue (FACT-F)
http://www.acsm-tj.org Translational Journal of the ACSM
DISCUSSION
Figure 2: EXACT study screening and recruitment for hematological
cancer, breast cancer, and total (summed) participants. Percentages
are relative to total screened per group. Medical appr., medical approval.
vs 34.3 ± 3.2 mL·kg⁻¹·min⁻¹; Fig. 3A). Although no changes
were found at the group level, varied responses in AET were
observed at the participant level and mediated changes in aero-
bic fitness. Four participants increased their aerobic fitness ≥ 1
MET (3.5 mL·kg⁻¹·min⁻¹; an average improvement of 14%),
four participants decreased ≥ 1 MET (an average decline of
16%), and one participant changed <1 MET. Interestingly,
neither improvement nor decline in aerobic fitness correlated with
session adherence (R² = 0.06; Fig. 3B).
No changes in total or domain-specific quality of life (FACT-G),
ilness (FACT-B and -Lym), or therapy-related fatigue (FACT-F)
were noted (Fig. 4A–H). Lastly, there were no statistically signifi-
cant differences between pre- and postintervention serum levels
of IL-1β, IL-6, TNF-α, and VEGF (P > 0.05; Fig. 5A–D).

DISCUSSION
This study aimed to determine the following: 1) the feasi-
bility of a 12-wk AET intervention for individuals with cancer
receiving ACs at the largest tertiary healthcare center in Atlan-
tic Canada and 2) the preliminary efficacy of the AET interven-
tion on participant cardiac and quality of life outcomes.
Approximately 29% of individuals screened for the study were
eligible to participate. In five clinical exercise trials conducted
with individuals with cancer using an intervention similar to
the one used in the present study (i.e., a nonlinear AET inter-
vention), the number of eligible participants recruited ranged
from 25% to 67%, with an average of 45% (39–43). Although
the proportion of eligible individuals in the current study was
relatively low, it does fall within the range of comparator
studies. Of note, the present study recruited 15 participants
per year, whereas the comparator studies recruited an average
of 18.5 per year (range, 7–40). The present study recruited a
similar number of participants in relative terms, suggesting
that participant accrual was noninferior in comparison with
patient accrual at other cancer centers. Among the difficulties
of recruiting, travel distance was the most limiting factor in
the present study. This was also a major limiting factor to
recruitment in the five comparator studies (39–43). Thus,
AET/study sites local to the population being studied as well
as ease of access and transportation are extremely important
for the successful recruitment of cancer participants. Furthermore,
widely eligible criteria (e.g., expanding the time limits regarding
when participants first received ACs, fewer contraindicated
comorbidities, etc.) may also help promote better recruitment.
It should be noted that 89% of study participants met
physical activity guidelines at enrollment as determined by
the IPAQ. This is higher than the national average meeting
guidelines, which is 18% for Canadian adults (44). The
discrepancy between what is reported in the study versus the
national average may be because those that already perform
regular physical are more likely to participate in research
involving exercise or attributed limitations associated with
self-report measures like the IPAQ. Several studies have
shown that the IPAQ overestimates physical activity levels in
comparison with objective measures (45,46). Thus, it is possible
that fewer participants than indicated by the IPAQ were
meeting the activity guidelines. In future studies, considera-
tion should be given to using objective measures to better determine
the physical activity levels of participants.
Retention for the present study was 67% (i.e., 10 of 15 partic-
ipants consented and completed the study), which was slightly
below the average of the five comparator studies (84% ± 9%)
although within their range (65%–100%). The reported session
adherence of 73% also falls below the average of five comparator
studies (80% ± 6%) but still within their range (72%–85%
[39–43]). Of note, there was a single participant that only
attended 2 of the 24 exercise sessions because of reported
treatment-related side effects. When these participants’ data were
removed, intervention adherence improved to 80%. The
similarity in feasibility statistics between this study and comparator
studies suggests that the largest cancer care center in Nova Scotia
is comparable with the other studies with respect to participant
accredural, adherence, and retention. Further, there were no
exercise-related adverse events reported, which is congruent
with the other studies which reported minimal safety concerns
(39–43). This intervention therefore does not appear to pose a
significant injury risk for individuals with cancer receiving ACs.
In addition to feasibility, this study also assessed efficacy-
related outcomes. AC treatment is typically associated with
decreased levels of fitness, increased levels of inflammation,
and decreased quality of life (5–7,43). This study found that
the average postintervention peak estimated aerobic fitness
remained unchanged, suggesting that AET may have mitigated
losses in aerobic fitness in the presence of ACs. This will need
to be confirmed in a future study using a control group. This
contrasts with other studies that found AET interventions
increased aerobic fitness in individuals with cancer, although
none of these participants were reported to be receiving ACs
(39–41,47). The starting fitness (i.e., peak estimated aerobic
fitness at baseline) of the participants in the present study was
| TABLE 1.  
Participant Characteristics. |
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<tr>
<td><strong>Breast (n = 7)</strong></td>
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<td>-----------------------------</td>
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<tr>
<td>Age (yr)</td>
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<td>Sex (M/F)</td>
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<td>Height (cm)</td>
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| **Pre** | **Post** | **Pre** | **Post** | **Pre** | **Post** |
|-----------------------------|
| Weight (kg) | 79.1 ± 12.6 | 81.0 ± 13.2 | 88.7 ± 23.1 | 84.8 ± 19.6 | 82.0 ± 15.7 | 82.1 ± 14.3 | 0.937 | 0.009 |
| BMI (kg·m⁻²) | 29.8 ± 3.0 | 30.4 ± 3.1 | 29.2 ± 9.2 | 27.8 ± 7.6 | 29.6 ± 5.0 | 29.6 ± 4.5 | 0.999 | 1.69E−05 |
| Waist circumference (cm) | 96.8 ± 8.3 | 96.4 ± 9.0 | 96.7 ± 24 | 97.3 ± 13.4 | 96.8 ± 13.2 | 96.65 ± 11.4 | 0.928 | 0.012 |
| Resting systolic blood pressure (mm Hg) | 115 ± 12 | 123 ± 13 | 130 ± 27 | 130 ± 31* | 119 ± 18 | 124 ± 16* | 0.407 | 0.321 |
| Peak systolic blood pressure (mm Hg) | 160 ± 13 | 155 ± 17 | 187 ± 27 | 160 ± 14 | 168 ± 21 | 157 ± 15 | 0.145 | −0.643 |
| Resting diastolic blood pressure (mm Hg) | 76 ± 8 | 75 ± 10 | 77 ± 17 | 87 ± 30* | 76 ± 10 | 78 ± 15* | 0.981 | 0.145 |
| Peak diastolic blood pressure (mm Hg) | 77 ± 3 | 75 ± 5 | 81 ± 8 | 80 ± 14 | 78 ± 5 | 77 ± 8 | 0.318 | −0.232 |
| Resting heart rate (bpm) | 83.9 ± 20.6 | 89.1 ± 8.7 | 84.0 ± 26.2 | 76 ± 0* | 83.9 ± 20.9 | 86.2 ± 9.5 | 0.430 | 0.143 |
| Peak heart rate (bpm) | 160 ± 23 | 152 ± 22 | 174 ± 6 | 164 ± 3 | 164 ± 20 | 156 ± 18 | 0.004 | −0.420 |
| Resting rate pressure product (mm Hg·bpm⁻¹·min⁻¹) | 9,577 ± 2,163 | 10,912 ± 1,714 | 10,770 ± 3,201 | 9,880 ± 2,365 | 9,935 ± 2,394 | 10,655 ± 1,768 | 0.091 | 0.342 |
| Peak rate pressure product (mm Hg·bpm⁻¹·min⁻¹) | 25,691 ± 4,410 | 23,847 ± 6,002 | 32,455 ± 3,833 | 26,220 ± 1,867 | 27,720 ± 5,187 | 24,638 ± 4,880 | 0.053 | −0.612 |
| Met activity guidelines (Y/N) | 5/1* | 6/0* | 3/3 | 3/3 | 8/9* | 9/9* |
| Activity levels (MET·min·wk⁻¹) | 3,167 (986–4,422) | 3,036 (1,344–8,625) | 10,118 (8,346–14,844) | 4,209 (2,313–13,282) | 4,311 (1,759–9,232) | 3,408 (1,938–8,717) | 0.793 | 0.086 |
| Estimated VO₂peak (mL·kg⁻¹·min⁻¹) | 28.5 ± 4.8 | 28.8 ± 5.0 | 45.9 ± 6.7 | 45.3 ± 8.1 | 33.67 ± 9.8 | 34.3 ± 10.0 | 0.891 | 0.064 |

Pre- and postvalues for all subjects pooled together were nonsignificant (P > 0.05). Values are presented as mean ± SD except for activity levels, which are median (25th–75th percentile). Cohen’s d convention interpretation reference: 0.2 = small, 0.5 = medium, and 0.8 = large (28).

* n − 1; individual’s records were unclear.
M, male; F, female.
Figure 3: A. Peak estimated aerobic fitness ($\dot{V}O_2$ [mL·kg$^{-1}$·min$^{-1}$]; mean ± SD) achieved during a submaximal ramped aerobic treadmill-based stress test. B. Regression analysis between attendance, presented as a percentage of recommended sessions, and absolute peak $\dot{V}O_2$ change revealed no changes pre- to postintervention. $n = 9^*$. $r^2 = 0.06$. Note: P1 was unable to complete their postintervention stress test. C. Physical activity in MET-minutes (mean ± SD) estimated using the long form of the IPAQ.
not associated with changes in fitness after the intervention (data not shown), which suggests that other determinants played a role. Fitness gains observed in other studies and not the present may be due to differences in training methods. In studies where aerobic fitness gains were reported, participants exercised three (40,41) or even five (39,47) times per week. In comparison, participants in the present study only exercised twice per week; thus, the cumulative volume of exercise per week was greater in the comparator studies and may have elicited a stronger fitness response. The lower training volume in the current study may also explain why some participants did not experience any fitness gains (Fig. 2B). Future work should consider the increasing the training volume in an effort to improve fitness levels. An alternative would be to recruit individuals who are sedentary or perform low levels of physical activity as it has been shown they typically exhibit the greatest gains and benefits from starting an exercise program (48). It is a limitation that we were unable to use gas analysis, which would have allowed a more accurate recording of peak aerobic fitness, and instead used proprietary formulas from the Case system. Notwithstanding,

Figure 4: Functional Assessment of Cancer Tools (FACT) for all participants pre- to postintervention (n = 10; mean ± SD). (A–E) FACT-G (General Measures) scores for each of its four constituents. FACT-G (P = 0.113, Cohen’s d = −0.568); physical subsection (P = 0.184, Cohen’s d = −0.500); social subsection (P = 0.353, Cohen’s d = −0.469); emotional subsection (P = 0.174, Cohen’s d = −0.555); functional subsection (P = 0.929, Cohen’s d = 0.071). (F, G) FACT questionnaire scores for hematological cancer–specific functional assessment questions (FACT-Lym; n = 3, P = 0.223, Cohen’s d = −1.96) and breast cancer–specific functional assessment questions (FACT-B; n = 7, P = 0.743, Cohen’s d = −0.145). (H) Functional assessment of chronic illness therapy fatigue scale (FACT-F; P = 0.521, Cohen’s d = −0.069). Note: FACT-B and FACT-Lym have different questions and are thus noncomparable.

Figure 5: Pre- and postintervention serum cytokine levels for all participants (n = 10; mean ± SD). Wilcoxon signed rank test P values are provided. A. IL-1β (P = 0.881; Cohen’s d = 0.514). B. IL-6 (P = 0.093; Cohen’s d = 0.823). C. TNF-α (P = 0.610; Cohen’s d = 0.708). D. VEGF (P = 0.841; Cohen’s d = −0.134).
not all participants in comparator studies were receiving ACs, and therefore their cardiotoxic risk profiles would likely differ from the participants in the present study. Although some participants experienced improved aerobic fitness where others experienced declines, the net effect was an absence of change in aerobic fitness. This suggests that AET may have been cardioprotective in some, but that a greater training volume may be required to achieve cardioprotection/improve aerobic fitness in others. Thus, larger randomized controlled trials are required to investigate these differences between individual response and training volume.

Chemotherapy can result in increased levels of fatigue and negatively influence quality of life in individuals with cancer. Overall, baseline levels of fatigue and quality of life remained unchanged over the course of the study. Similar results were reported in another study, which used a nonlinear aerobic exercise intervention involving individuals with breast cancer (43). By contrast, other studies have reported improvements in both fatigue and quality of life after AET (42,49). The difference in results between these studies and the present work may be partially explained by differences in total training volume, or in stage/type of cancer, antineoplastic treatments received, and current lifestyles of participants (50). However, the lack of changes in quality of life or overall fatigue levels suggests the AET intervention may have mitigated adverse treatment-related side effects. It is important to note that the FACT-F was not capable of registering daily variations in fatigue that led some participants to miss exercise sessions. Future trials may consider measuring fatigue more frequently throughout the intervention to better understand how AET is influenced by chemotherapy-related fatigue and vice versa.

Because AC-mediated cardiotoxicity is related to inflammation (5,51), we investigated the effects of AET on systemic levels of inflammatory cytokines. In the present study, no statistically significant difference was observed between pre- and postintervention levels of serum IL-1β, IL-6, and TNF-α. Similarly, VEGF, which was expected to increase during AC therapy, did not (31). Overall, the results suggest that the AET intervention prevented an AC-mediated increase in inflammation. However, the sample size of this study was small; thus, care must be taken when interpreting the results. In fact, effect sizes for the various cytokines suggest that an increase in inflammation may have been observed with a larger sample. Of note, the present study did not have a control group, so it was not possible to determine whether AET attenuated AC-mediated inflammation. In the future, studies that are powered to look at inflammatory markers and that use a control group are needed to determine the effect of AET on AC-mediated inflammation.

This study demonstrated that progressive nonlinear AET appears feasible for individuals receiving AC-based therapy with high levels of fatigue and that AET may have a positive effect on several AC-related side effects. However, given the small sample and lack of control group, caution must be exercised when interpreting the overall intervention efficacy. A larger RCT study that includes a control group and stratifies participants based on age, sex, cancer, treatment, etc., would be a natural progression. The addition of other cardiotoxic biomarkers (i.e., troponin I and N-terminal pro B-type natriuretic peptide) would also strengthen future work by enabling comparison with other trials that have studied AC-mediated cardiac damage. To truly evaluate the potential cardioprotective ability of AET, a more direct assessment of cardiac function and structure via imaging (e.g., echocardiography, MRI) is required. Furthermore, future studies should consider using single CPET protocol as well as analyze expired gases. Although the recruitment rate in his study was similar to other exercise trials in cancer populations, participant accrual remains challenging. The primary barrier to participation was the inconvenience of traveling to and from the exercise training site. This influenced recruitment by clinicians who chose not to ask 19 eligible participants if they would be willing to participate in the trial as they believed they lived too far away. In terms of those eligible participants approached, 53% declined noting travel time as the primary reason for not wanting to participate. As travel was a significant barrier to participation, future studies may wish to consider how AET can be delivered remotely. In the follow-up to this study, EXACT 2.0 (recruiting; NCT03748550) participants are given a home-based exercise program and are followed remotely. Another possibility would be to use mobile health technologies. Several smartphone applications have been developed to help provide exercise programming to individuals unable to attend in-person sessions. Incorporation of this type of technology could vastly improve accrual in future exercise trials.

**Conclusion**

In summary, the present study was deemed feasible at the Nova Scotia healthcare center where it was conducted. It was not inferior in recruitment, retention, adherence, or safety in comparison with similar exercise interventions involving individuals with cancer performing a nonlinear AET intervention. Travel distance and perceived inconvenience remained the largest barriers to recruitment in this study.

AET may have attenuated adverse changes in fatigue and quality of life associated with ACs. It may also have prevented/minimized changes in AC-mediated inflammation. A growing number of human trials are investigating the role of AET to prevent or mitigate AC-mediated cardiotoxicity, which continues to be a significant concern for individuals with cancer receiving ACs. Together, these results suggest the AET performed while on AC treatment is safe and feasible and can also maintain the physical fitness and quality of life of the patient. The results from this trial have enabled the beginning of a larger randomized controlled trial at the same healthcare center investigating an AET intervention for individuals with cancer receiving ACs (ClinicalTrials.gov: NCT03748550). Finally, there were several lessons learned from this research, specifically regarding participant recruitment and the location of AET. Future research and clinical exercise programs need to develop methods to target those cancer survivors who do not meet physical activity guidelines as well as methods to offer AET remotely to engage those who cannot travel or do not want to travel.

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