“Chemotherapy-periodized” Exercise to Accommodate for Cyclical Variation in Fatigue

Amy A Kirkham1, Kelcey A Bland2, David S. Zucker3, Joshua Bovard4, Tamara Shenkier5, Donald C McKenzie4, Margot K Davis6, Karen A Gelmon5, Kristin L Campbell2,7

1Department of Biomedical Engineering, University of Alberta, Edmonton, Canada; 2Rehabilitation Sciences Program, University of British Columbia, Vancouver, Canada; 3Cancer Rehabilitation Medicine Services, Swedish Cancer Institute, Swedish Health Services, Seattle, WA; 4School of Kinesiology, University of British Columbia, Vancouver, Canada; 5Medical Oncology, British Columbia Cancer Agency, Vancouver, Canada; 6Division of Cardiology, University of British Columbia, Vancouver, Canada; 7Department of Physical Therapy, University of British Columbia, Vancouver, Canada

Accepted for Publication: 30 August 2019

Medicine & Science in Sports & Exercise® Published ahead of Print contains articles in unedited manuscript form that have been peer reviewed and accepted for publication. This manuscript will undergo copyediting, page composition, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered that could affect the content.

Copyright © 2019 American College of Sports Medicine
“Chemotherapy-periodized” Exercise to Accommodate for Cyclical Variation in Fatigue

Amy A Kirkham¹, Kelcey A Bland², David S. Zucker³, Joshua Bovard⁴, Tamara Shenkier⁵, Donald C McKenzie⁴, Margot K Davis⁶, Karen A Gelmon⁵, Kristin L Campbell²,⁷

¹ Department of Biomedical Engineering, University of Alberta, Edmonton, Canada
² Rehabilitation Sciences Program, University of British Columbia, Vancouver, Canada
³ Cancer Rehabilitation Medicine Services, Swedish Cancer Institute, Swedish Health Services, Seattle, WA
⁴ School of Kinesiology, University of British Columbia, Vancouver, Canada
⁵ Medical Oncology, British Columbia Cancer Agency, Vancouver, Canada
⁶ Division of Cardiology, University of British Columbia, Vancouver, Canada
⁷ Department of Physical Therapy, University of British Columbia, Vancouver, Canada

The first two authors contributed equally.
Corresponding author:

Dr. Kristin Campbell

212-2177 Wesbrook Mall, Vancouver, Canada V6T1Z3

Ph:(604)-827-4704; Fx:(604)-822-1870; E:Kristin.Campbell@ubc.ca

AK was supported by a Doctoral Award from the Canadian Institutes of Health Research and a Four-year fellowship from the University of British Columbia. Conflict of interest: The authors have no conflicts of interest to disclose. The results of the present study do not constitute endorsement by ACSM. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.
Abstract

PURPOSE: The purpose of this study was to provide a rationale for ‘chemotherapy-periodized’ exercise by characterizing cyclical variations in fatigue and exercise response across a chemotherapy cycle and comparing exercise adherence during chemotherapy between a prescription that is periodized according to chemotherapy cycle length and a standard linearly progressed prescription. METHODS: Women with breast cancer who were prescribed taxane-based chemotherapy were randomly assigned to a supervised aerobic and resistance exercise program following a chemotherapy-periodized exercise prescription (n=12) or to usual care during chemotherapy (n=15). Fatigue and steady state exercise responses were assessed in both groups prior to the first taxane treatment and across the third treatment (i.e., 0-3 days prior and 3-5 days after the third treatment, and 0-3 days prior to the fourth treatment) to assess cyclical variations. Adherence to the chemotherapy-periodized exercise prescription was compared to adherence to a standard linear prescription from a prior study in a similar population (n=51). RESULTS: Fatigue increased from baseline (marginal mean±standard error: 3.2±0.4) to prior to the third treatment (4.1±0.4, p=0.025), then peaked at 3-5 days after the third treatment (5.1±0.4, p=0.001), before recovering prior to the next treatment (4.3±0.5, p=0.021). The peak in fatigue at 3-5 days post-third treatment corresponded to a decrease in steady state exercise oxygen consumption (VO₂) (p=0.013). Compared to a standard linear exercise prescription during chemotherapy, a chemotherapy-periodized exercise prescription resulted in higher attendance during the week after chemotherapy (57±30% vs 77±28%, p=0.04) and overall attendance (63±25% vs 78±23%, p=0.05). CONCLUSION: Fatigue and exercise VO₂ vary across a chemotherapy cycle. A chemotherapy-periodized exercise prescription that accommodates cyclical variations in fatigue may increase adherence to supervised exercise.
**Keywords:** breast cancer; periodization; exercise training; side effects;
Introduction

There are numerous benefits of supervised exercise training during chemotherapy for women with early stage breast cancer, including better quality of life, reduced treatment symptoms and improved physical fitness (1). Engaging in regular exercise during chemotherapy is arguably more challenging relative to other phases of the treatment trajectory due to common and debilitating physical side effects, such as peripheral neuropathy, arthralgias or myalgias, fatigue, and nausea (2-5). In fact, treatment symptoms are the most commonly reported barrier to adherence to exercise during chemotherapy treatment for women with breast cancer (6).

Chemotherapy treatment for breast cancer is typically delivered by a series of infusions separated by one, two, or three weeks, known as a cycle. The pattern of onset, duration and intensity of side effects following chemotherapy infusions varies from patient to patient. In the first 7 days after each infusion, increased feelings of fatigue and depression, as well as elevated resting heart rate, reduced blood pressure, and sleep disturbances have been reported (7-9). This time period is also in parallel to when chemotherapy agents are biologically active before being cleared from the body (10,11). During this time, a patient’s physical capacity and willingness to engage in exercise, along with the biological activity of treatment, suggest that a lower relative intensity aerobic exercise prescription could be less likely to exacerbate the acute side effects such as nausea or fatigue, or to augment oxidative stress to healthy tissues in addition to that caused by chemotherapy. Patients then tend to experience steady improvements in their treatment symptoms and a period of relative recovery before their subsequent chemotherapy
infusion (7-9). However, due to the cumulative nature of chemotherapy side effects, patients are unlikely return to the same physical baseline experienced prior to commencing chemotherapy. A hypothesized schematic of these cyclical variations and accumulation of treatment symptoms is shown in Figure 1.

Periodization is an organizational approach to aerobic and resistance training often used in high performance populations that involves short cycles or ‘periods’ of systematic variation in training specificity, intensity, or volume (12). Periodized training incorporates progressive overload, recovery, and variations in training stimulus with the goal of maximizing physiological fitness improvements by incorporating optimal recovery to prevent severe fatigue and injury and has been used successfully in trained athletes, untrained adults, and injured adults (13,14). Given the cyclical variations in cancer treatment side effects, an exercise prescription that is periodized to chemotherapy treatment cycles may be a successful approach to optimize physiological benefits of exercise. Promoting consistency of training throughout chemotherapy treatment by preventing a gap in attendance following every chemotherapy treatment may increase overall program attendance and thereby enhance the impact of exercise training on key patient-reported and fitness outcomes.

The EXercise Influence on Taxane side effects (EXIT) trial was a randomized controlled trial with a primary aim of determining if multi-modal exercise training during taxane-based chemotherapy for early stage breast cancer could mitigate chemotherapy-induced peripheral neuropathy (15). This manuscript represents a secondary aim of the EXIT trial to provide a rationale for ‘chemotherapy-periodized’ exercise by: 1) characterizing cyclical variations in cancer treatment fatigue and exercise response across a chemotherapy cycle; and 2) comparing
exercise adherence metrics during chemotherapy between a prescription that is periodized to chemotherapy cycle length and a standard linearly progressed prescription.

Methods

Design

The EXIT trial was a 2-arm randomized controlled trial where participants were randomly assigned to complete an immediate ‘chemotherapy-periodized’ exercise intervention concurrent to their taxane-based chemotherapy (immediate exercise group) or to usual care. The usual care group then participated in a ‘periodized’ exercise intervention that was identical to that performed during chemotherapy but was delayed until completion of their taxane-based chemotherapy (delayed exercise group). Data for the characterization of fluctuations in fatigue and exercise response during chemotherapy was collected for both groups in EXIT during their taxane-based chemotherapy treatments. To compare adherence between ‘chemotherapy-periodized’ and standard linear exercise prescriptions, data from the immediate exercise group from the EXIT trial was compared against the previously completed Nutrition and Exercise during adjuvant Treatment (NExT) single-arm trial that employed a standard linear prescription during chemotherapy in women with breast cancer (6,7,16,17). A schematic of the two trial designs is depicted in Figure 2. Both the EXIT and NExT studies were performed by the same research staff, with the same supervision procedures, in the same location, with the same referring oncologists, and have comparable participants with no overlap in recruitment. Both studies were approved by research ethics boards and all participants signed informed consent.

Participants

Participants in both trials were recruited via oncologist referral, posters, and word-of-mouth. EXIT participants were recruited between 2015-2017 and inclusion criteria were English-
speaking adult women with stage I-III breast cancer who were scheduled to receive paclitaxel- or docetaxel-based adjuvant or neoadjuvant chemotherapy. Exclusion criteria were stage IV cancer, acute or uncontrolled health conditions, diabetes, history of a neurological disorder, body mass index >40 kg/m$^2$, chemotherapy prescribed in a weekly format, or previous cancer diagnosis. NExT participants were recruited between 2013-2014 and inclusion and exclusion criteria were comparable to the EXIT trial except that only adjuvant patients were included, and participants were not excluded if they had a previous cancer diagnosis, a diagnosis of stable diabetes, or a neurological disorder. For this analysis, only the NExT participants receiving comparable chemotherapy protocols (namely taxane-based chemotherapy in biweekly or triweekly format) were included in this analysis. To match the timing of exercise intervention delivery in EXIT, adherence data from NExT were only included from the time when participants were undergoing taxane-based portions of their chemotherapy protocols.

Exercise prescriptions

Initiation of training: EXIT participants randomized to the immediate exercise group could start the exercise intervention up to one week prior to the first taxane-based treatment and the exercise prescription aligned with their chemotherapy treatment dates. Participants randomized to the delayed exercise group could start the exercise intervention two weeks after the last taxane-based chemotherapy treatment, but neoadjuvant patients or patients undergoing second surgeries waited 4-6 weeks post-surgery before beginning the exercise intervention. In NExT, participants were eligible to start the intervention before completing 50% of their chemotherapy treatment (any type) and up to two weeks prior to their first chemotherapy
treatment. Therefore, the beginning of the linear exercise prescription delivered in NExT in relation to chemotherapy treatment number and timing within a cycle was completely random and varied widely between participants.

Program length: For EXIT, the exercise intervention length matched the length of participants’ taxane protocol regardless of group assignment, which was 8-12 weeks. Data from the matching period was used from NExT.

Type: Participants in both studies performed supervised aerobic and whole-body resistance exercise training. Aerobic training could be performed on a treadmill, cycle ergometer, or elliptical trainer. Resistance training exercises in NExT included leg press, leg curls, calf raises, chest press, and seated row using resistance machines, dumbbells or resistance bands, as well as two core-strengthening exercises. The EXIT resistance exercises were identical except that chest press was performed with a resistance band, and leg curls were removed to allow time for hand, foot and balance exercises targeted for the study’s primary outcome of peripheral neuropathy.

Frequency: Participants in both studies were offered three supervised sessions per week. Participants were encouraged to perform two home-based sessions of aerobic exercise starting in week three or four of the program, depending on comfort level.

Aerobic intensity: Both studies used percentage of age-predicted heart rate reserve (HRR) with recently measured resting heart rate values to prescribe aerobic exercise intensity. Figure 2 depicts the aerobic intensity and duration prescriptions used in each study. For the chemotherapy periodization approach used in EXIT, periods were matched in length to each participant’s chemotherapy protocol (2 or 3 weeks in length). For the immediate exercise group in EXIT, the first week of each period corresponded to the 7 days immediately after each chemotherapy...
treatment. The aerobic exercise intensity was set at 50-55% HRR for the first week in each period for both groups in EXIT. The goals of this pre-emptively reduced intensity during chemotherapy weeks were to: 1) encourage participants to attend during this week where their treatment symptoms will be the most intense; 2) prescribe manageable exercise in the presence of symptoms and/or not exacerbate active symptoms such as nausea, muscle or bone pain, or fatigue; and 3) not increase oxidative stress in healthy cells in addition to that caused by chemotherapy. For the delayed exercise group (i.e., exercise post-chemotherapy) in EXIT, this week represented a traditional “rest” or recovery week. In the remaining weeks of each cycle (either 1 or 2 weeks, depending on chemotherapy protocol), the aerobic intensity was progressed by 5% HRR from the previous cycle’s last intensity level to induce overload during this period when the participant was less burdened by treatment side effects. In contrast, for NExT, the intensity started at 50-55% HRR when participants joined the study and was linearly progressed by 5% HRR every two weeks.

Aerobic duration: For EXIT, with the exception of the week following initiation of the first treatment cycle (25 minutes), exercise duration was increased to 40 minutes during the first week following infusion of each subsequent chemotherapy cycle for the immediate exercise group to maintain the volume of exercise in view of the reduced exercise intensity (Figure 2). The same was done for the first week of each period for the delayed exercise group. In the remaining weeks of each cycle, the aerobic duration was prescribed as 30-35 minutes to allow for the progression in aerobic intensity during these weeks. For NExT, the aerobic duration was 20 minutes for the first week, 25 minutes for the second and third weeks, and 30 minutes thereafter.
Resistance repetitions, sets, and weight: For resistance training intensity, the same submaximal strength test was used to estimate one-repetition maximum (1-RM) for leg press in both studies (18). Both studies started with one set of 10-12 repetitions of leg press at 50% of 1-RM. All other resistance machine or dumbbell exercises were started with a similar prescription at a weight that felt subjectively similar in perceived exertion to the leg press prescription. If resistance bands were used instead, the easiest band was used to start. For EXIT, the resistance prescription was maintained at one set at 50% 1-RM (with similar intensity on other exercises) for the week after every chemotherapy infusion for the immediate exercise group or the first week of each period for the delayed exercise groups. This was done to reduce intensity similar to the aerobic prescription, as well as to reduce total resistance training duration to allow for the longer aerobic duration during these weeks. In the following week of each chemotherapy cycle or training period, two sets of 8-10 repetitions at a weight progressed by 5% 1-RM (or equivalent) was performed. For patients with a three-week cycle, two sets of 10-12 repetitions at the same weight was performed the following week. For NExT, after the first week, two sets of 10-12 repetitions were consistently prescribed every week and weight was linearly progressed by 5% 1-RM every two weeks.

Outcome measures

To characterize the cyclical variations with a chemotherapy cycle in the EXIT trial, participants in both groups (i.e. immediate exercise group or delayed exercise group who received usual care during taxane chemotherapy) completed a fatigue questionnaire and a submaximal steady state exercise test at: 1) baseline (0-14 days prior to the first taxane-based chemotherapy treatment), and at three additional time points across the third chemotherapy cycle to detect cyclical variations in outcomes as follows: 2) 0-3 days prior to taxane cycle 3; 3) 3-5
days after taxane cycle 3; and 4) 0-3 days prior to taxane cycle 4. Fatigue was assessed by the total fatigue score from the revised Piper Fatigue scale (19). Total fatigue was calculated by adding scores from all 22 items and then dividing by 22, to provide a total score on a 0-10 numeric scale. The exercise test started with two minutes of quiet seated rest on an upright cycle ergometer, followed by 10 minutes of exercise at an absolute workload of 60 watts. The volume of oxygen consumption ($\text{VO}_2$) and heart rate at rest and during exercise with a fixed load were continuously measured (Fitmate Pro, Cosmed, Concord, CA and Finometer® PRO, FMS, Amsterdam, The Netherlands, respectively). Participants were instructed to maintain their pedaling frequency as close to 80 repetitions per minute as possible at all sessions. Participants were asked to indicate their subjective rating of perceived exertion (RPE) just prior to the completion of the 10-minute bout using a Borg 6-20 scale (20). Resting $\text{VO}_2$ and heart rate were taken as the average from 0.5 to 2 minutes during the rest period, whereas steady state $\text{VO}_2$ and heart rate were taken as the average from six minutes into exercise (to ensure steady state in all participants) to the end of the 10-minute period of exercise.

Exercise adherence variables were calculated as percentages using the same methods for both the EXIT and NExT studies. Attendance was calculated as the number of sessions attended divided by the number of sessions prescribed for the period of interest. Adherence to aerobic intensity and duration were calculated as the number of sessions where the minimum heart rate or duration target was met out of the number of sessions attended. Adherence to resistance training was defined as the percentage of sessions where all exercises were performed according to prescribed sets, repetitions and weight. Any deviation from these parameters was considered as adherence not met. Adherence to completion of each type of resistance exercise was previously reported to be ubiquitously high (89-96%) in NExT (6), so adherence was only
collected for the program as a whole for EXIT. Barriers to attendance were collected by self-report from participants following a missed session.

Statistics

Linear mixed models or generalized linear mixed models were used to evaluate outcomes between the EXIT groups (i.e., chemotherapy-periodized exercise vs. usual care) over time (group by time interaction). Participant was included as a random effect in all models to account for correlations across time (21). For generalized models, a link function and distribution that resulted in normality of model residuals, or that produced the best model fit, were selected for each outcome. In the case of non-significant interactions, the time main effect was interpreted. Post-hoc pairwise contrasts were used to assess whether differences exist between consecutive time points (i.e., baseline vs prior to third cycle, prior to third cycle vs 3-5 days after third cycle, 3-5 days after third cycle vs prior to fourth cycle) either for each group independently or both groups combined (depending on presence of an interaction effect). P-values of 0.05 were used to indicate statistical significance.

Exercise adherence variables were compared between groups using independent t-tests. Adherence variables were also compared between chemotherapy and non-chemotherapy weeks for the same prescription with paired t-tests. For both tests, two-tailed p-values of 0.05 were used to indicate statistical significance. Corrections for multiple comparisons were not made.

Results

Participants

The flow through the studies have been previously reported in detail (15,16). In EXIT, 15 participants were randomized to the immediate exercise group and 16 participants were assigned to the delayed exercise group. Three participants became ineligible after randomization and one
withdrew due to personal reasons, leaving n=12 and n=15 in the immediate and delayed groups. In NExT, 73 total participants enrolled, and 51 of these received comparable taxane-based chemotherapy protocols to EXIT and attended at least one exercise session during the period of interest. Participants in both groups of EXIT and in NExT were comparable at baseline (Table 1).

Characterization of cyclical changes in fatigue and exercise responses during chemotherapy

Fatigue did not vary by EXIT group over time (p=0.336), but there was a main effect for time (p=0.006). The pattern of fatigue over the third treatment cycle was in line with the hypothesized cyclical pattern across a chemotherapy cycle (Figure 3). Fatigue increased from baseline (marginal mean±standard error: 3.2±0.4) to prior to the third cycle (4.1±0.4, p=0.025), then further increased and peaked 3-5 days after the third cycle (5.1±0.4, p=0.001), before decreasing just prior to the fourth cycle (4.3±0.5, p=0.021), where it was still higher than baseline (p=0.029).

Absolute and relative resting VO\textsubscript{2} and heart rate did not vary by group over time nor by time independent of group (all p>0.207). Exercise heart rate and RPE also did not vary by group over time (p=0.193, p=0.467) nor by time independent of group (p=0.129, p=0.212). Absolute and relative exercise VO\textsubscript{2} varied over time by EXIT group (p=0.051, p=0.036, respectively). During usual care (i.e., delayed exercise group only receiving exercise post-chemotherapy), both absolute and relative exercise VO\textsubscript{2} did not change between baseline (1140±44 mL/min, 17.3±0.7 mL/kg/min) and prior to the third cycle (1186±43 mL/min, p=0.275; 17.3±0.6 mL/kg/min, p=0.995), but decreased at 3-5 days after the third cycle (1075±37 mL/min, p=0.013; 15.8±0.6, p=0.007), followed by an increase just prior to the fourth cycle (1185±35 mL/min, p=0.001; 17.3±0.6, p=0.003). Prior to the fourth cycle, absolute and relative exercise VO\textsubscript{2} were not
different than baseline (p=0.086, p=0.986). With chemotherapy-periodized exercise, absolute and relative exercise VO$_2$ did not change across these time points (all p>0.064).

Comparison of adherence to a chemotherapy-periodized versus standard linear exercise prescription during chemotherapy

*Exercise frequency:* The comparisons of exercise adherence within and between prescriptions are provided in Table 2. Participants had higher overall attendance during chemotherapy with the chemotherapy-periodized prescription in EXIT (78±23%) compared to the standard linear prescription used in NExT (63±25%, p=0.05). During the standard linear prescription in NExT, attendance was lower during chemotherapy weeks (57±30%) than non-chemotherapy weeks (65±26%, p=0.01); whereas during the chemotherapy-periodized prescription in EXIT, no difference in attendance was found between weeks. During chemotherapy weeks, attendance was higher with a chemotherapy-periodized prescription compared to the standard linear prescription (77±28% vs 57±30%, p=0.04). During non-chemotherapy weeks, the chemotherapy-periodized prescription only trended toward higher attendance (79±21 vs 65±26%, p=0.09).

*Aerobic and resistance intensity and time:* Overall adherence to aerobic intensity and duration did not differ among prescriptions (Table 2). Adherence to prescribed aerobic intensity and duration did not differ between chemotherapy and non-chemotherapy weeks for the standard linear prescription. For the chemotherapy-periodized prescription, adherence to the prescribed aerobic intensity was higher during chemotherapy weeks (91±12%) than non-chemotherapy weeks (73±32%, p=0.05) and higher compared to chemotherapy weeks using the standard linear prescription (68±32, p<0.01). Adherence to the prescribed aerobic duration did not differ between weeks for the chemotherapy-periodized prescription. Adherence to resistance training
did not differ between chemotherapy and non-chemotherapy weeks for any prescription and was significantly lower for the standard linear prescription (overall: 50±37) relative to the chemotherapy-periodized prescription (overall: 78±37, p=0.03).

Comparison of adherence to a “chemotherapy-periodized” prescription during chemotherapy versus regular periodized prescription post-chemotherapy

Adherence for frequency, intensity, time and type did not differ when EXIT participants completed an identical periodized exercise prescription during compared to post-chemotherapy (i.e., delayed exercise group) (Table 2).

Comparison of barriers to exercise adherence among all exercise prescriptions

Despite significantly lower prevalence of missed sessions, treatment symptoms were a more common barrier to attendance in the chemotherapy-periodized prescription in the immediate exercise group of EXIT compared to the standard linear prescription of NExT (Table 2). For EXIT, we also asked participants to provide the primary treatment symptom that was preventing them from attending exercise sessions. Fatigue was the most common symptom, accounting for 74% of all cases where treatment symptoms prevented attendance. Eight percent of cases were due to muscle or bone pain, and no cases were due to nausea or peripheral neuropathy. Vacation was a more frequent barrier to attendance in the delayed exercise group of EXIT (i.e., exercise post-chemotherapy). While cold/flu was an equally common barrier to attendance during chemotherapy in both EXIT and NExT, it was less common after chemotherapy. The primary barrier to attendance after chemotherapy in the delayed exercise group of EXIT was musculoskeletal injuries.
Discussion

Incorporation of the principles of exercise training, especially individualization, specificity, progressive overload, and rest/recovery, into an exercise prescription is a key component of efficacious exercise programming. Among the hundreds of exercise oncology trials published to-date, exercise interventions have almost always incorporated a standard linear approach to progressive overload (22). While evidence indicates this type of prescription is safe, feasible, and has benefits for the management of some chemotherapy side effects such as fatigue, whether this traditional approach is “optimal” for cancer populations is a topic of debate (22,23). Others have suggested that a non-linear approach to exercise prescription would optimize exercise adaptations in oncology populations, but those studies employing this technique to-date have not tailored the prescription to occurrence of cancer treatment side effects (22). The optimal exercise prescription to optimize physical and psychological benefits during active cancer treatment is unknown. During cancer treatment, important goals of an optimal exercise prescription include maximization of: 1) exercise adherence and uptake; 2) feasibility for implementation within real-world settings; and 3) physical and psychological benefits. In the current study, we implemented a chemotherapy-periodized exercise prescription with these goals in mind and assessed the impact on exercise adherence.

Aerobic and resistance exercise prescribed using traditional linear exercise prescriptions can be beneficial for fitness and quality of life during chemotherapy for early stage breast cancer (24). However, these generic exercise prescriptions may under-dose or over-dose exercise by failing to consider fluctuations in treatment side effects, exercise response and readiness to train. One objective of this manuscript was to systematically characterize variations in physical resting
and exercise response measures and patient-reported fatigue within a chemotherapy cycle that we and others have previously noted (7-9). To our knowledge, no other study has characterized both patient-reported and exercise responses in a systematic manner. As the number of assessments required to demonstrate cyclical variations is quite cumbersome for research participants and staff, we chose to characterize changes across the third (of four planned) chemotherapy cycles in the current study. The third chemotherapy cycle was chosen over the fourth to increase the probability of participant compliance, as treatment side effects are cumulative, and participants may be less able to attend assessments after the fourth treatment (6).

Patient-reported fatigue varied in cyclical manner similar to that hypothesized in Figure 1. There was an increase in fatigue from baseline to the end of the first two chemotherapy treatments, with a peak at 3-5 days after the third treatment (Figure 3), the acute time period we have previously noted to correspond to the peak of patient-reported symptoms. It is likely that this peak occurs following each treatment, but we only measured this acute response after the third treatment. Following this acute increase in fatigue, there was recovery to a level that was still higher than pre-treatment. Thus, readiness to train is likely lower the week immediately after chemotherapy and exercise progressions may be more tolerable (and potentially more effective) during the weeks following the week of infusion. Notably, while the interaction between group and time and was not statistically significant, the usual care group (who did not exercise during chemotherapy treatment) experienced changes in fatigue that appeared to be consistently higher than the immediate exercise group with a more pronounced peak. The immediate exercise training group experienced a similar trend in fatigue, but the magnitude of the changes appeared
to be more blunted. Thus, patients who do not regularly engage in exercise during chemotherapy, may experience a greater magnitude of an acute increase in symptoms.

The RPE and heart rate response to the steady state exercise bout did not statistically vary between groups or over time. Yet, Figure 3 depicts a trend for both variables where there was no change in the usual care group and a reduction in the immediate exercise group over time. Reductions in RPE and heart rate responses to the same workload over time would be indicative of a training adaptation. Furthermore, for resting heart rate, which we have previously shown to increase in the week after a given chemotherapy treatment (7), the exercise intervention may have blunted this elevation.

The significantly reduced steady state exercise VO$_2$ value at 3-5 days after the third treatment in the usual care group suggests an increase in efficiency (i.e., less VO$_2$ required to do same workload with same pedaling frequency) (25) or a greater relative anaerobic contribution to exercise. Given the short-lived change in VO$_2$ at 3-5 days after the third treatment (was increased again by the next time point 1-2 weeks later), it is likely that this change could be considered an acute metabolic change related to chemotherapy treatment. Unfortunately, the portable metabolic measurement system we used to assess VO$_2$ did not have a CO$_2$ analyzer, so we were unable to determine whether changes in substrate utilization contributed to this acute change. We are unable to explain the mechanism of this finding in the current study.

All breast cancer patients at the referring cancer treatment center are given the corticosteroid dexamethasone for 3 days starting the day before each docetaxel treatment or a single dose concurrent to paclitaxel treatment. Corticosteroids have been previously shown to increase VO$_2$ for a steady state cycling bout (26) rather than decrease as occurred in the current study. Patients receiving a bi-weekly chemotherapy regimen are also prescribed a granulocyte-colony
stimulating factor (G-CSF) to shorten the duration of neutropenia following each treatment. Five days of G-CSF following adjuvant chemotherapy was previously shown to significantly increase endothelial function measured via flow-mediated dilatation, but also markers of inflammation (IL-10, TNF-alpha, and C-reactive protein) relative to placebo (27). Either of these supportive therapies could potentially interact with the chemotherapy treatments and affect our measured outcomes. However, our sample size does not allow sub-group analyses to assess whether differences exist in those receiving these different supportive therapies.

We have previously reported for all participants on all chemotherapy protocol types in the NExT trial that treatment symptoms impact both exercise session attendance and exercise prescription adherence (6). In the EXIT trial, we tested the use of a periodized exercise prescription as a strategy to improve exercise attendance. One goal of the pre-emptive decrease in aerobic exercise intensity and resistance exercise session duration following each chemotherapy treatment was to encourage participants to attend exercise sessions when we anticipated treatment side effects to peak. Indeed, with a standard linear exercise prescription, adherence to the prescribed frequency was lower during chemotherapy weeks than non-chemotherapy weeks. Using the chemotherapy-periodized exercise prescription approach, adherence to the prescribed frequency was equivalent to that for non-chemotherapy weeks. In the chemotherapy weeks, adherence to the prescribed aerobic intensity, which was set at 50-55% HRR was extremely high (92% on average) and adherence to the prescribed duration, which was increased to 40 min to maintain volume, was equivalent to non-chemotherapy weeks (77 vs 79%). This indicates that these prescription parameters are highly tolerable for most patients even in the face of elevated fatigue. Furthermore, in comparing chemotherapy weeks between the periodized prescription and the standard linear prescription, adherence to the prescribed
exercise session frequency and aerobic intensity were higher and adherence to the prescribed aerobic duration was equivalent. Overall adherence to frequency was also higher with the chemotherapy-periodized approach. Adherence to all components of the resistance exercise prescription did not vary by chemotherapy versus non-chemotherapy weeks for either prescription but was significantly higher with the chemotherapy-periodized prescription. By all accounts, this analysis indicates that the chemotherapy-periodized exercise prescription resulted in significantly better exercise adherence by pre-emptively accommodating for cyclical variations in treatment side effects.

**Strengths and limitations:** All analyses reported in the current paper are exploratory in nature and are intended to generate hypotheses for future investigations on the utility of periodized exercise in cancer populations. The EXIT trial had a small sample size and was not powered based on the outcomes in the exploratory cyclical change analysis in the current manuscript. Despite this limitation, differences in trajectories between groups were apparent and were highlighted within this exploratory analysis to illustrate the concept of chemotherapy-related cyclical changes. The chemotherapy-periodized exercise prescription can be further refined and individualized for future interventions, including potential incorporation of higher-intensity aerobic interval training or higher intensity/volume resistance training during non-chemotherapy weeks. Ultimately, a combination of translating what is known from high quality sports performance interventions and understanding key cancer-treatment related physiological and patient-reported changes are necessary to make steps towards optimizing exercise prescriptions in cancer populations. A direct comparison between a periodized and linear exercise prescription within a randomized trial is needed to confirm our adherence findings and to compare efficacy of these different approaches for physical fitness and health outcomes.
In summary, exercise prescriptions utilized in most oncology studies to-date have not tried to accommodate for treatment-related fluctuations. In the current study, we utilized a chemotherapy-periodized approach to exercise during chemotherapy in women with early stage breast cancer and found that this prescription may optimize adherence by accommodating for treatment side effects. Findings reported in this paper provide a part of the foundation from which to further refine and target the optimal approach to exercise prescriptions within oncology populations.
Acknowledgements: The authors would like to acknowledge Alexandra Akl, Savanna Rowe, and Holly Wollmann for their assistance with exercise session supervision and data collection. AK was supported by a Doctoral Award from the Canadian Institutes of Health Research and a Four-year fellowship from the University of British Columbia.

Conflict of interest: The authors have no conflicts of interest to disclose. The results of the present study do not constitute endorsement by ACSM. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.
References


**Figure Legends**

Figure 1: Schematic of cyclical variations in treatment symptoms (or physical side effects) across four cycles of chemotherapy treatment. Blue arrows indicate timing of fatigue and oxygen consumption assessment to assess cyclical variations across cycle 3.

Figure 2: Schematic of the EXIT trial and NExT trial study designs (A) and aerobic exercise prescriptions (B). (A): Participants in the EXIT trial were randomized to an immediate exercise or delayed exercise (usual care during taxane chemotherapy) intervention. EXIT participants underwent additional assessments over the course of their taxane treatment to assess for cyclical variations during chemotherapy including 1) baseline (0-14 days prior to the first taxane-based chemotherapy treatment); 2) 0-3 days prior to taxane cycle 3; 3) 3-5 days after taxane cycle 3; and 4) 0-3 days prior to taxane cycle 4. The NExT trial was a single-arm, intervention study. (B) In NExT, the standard linear exercise prescription was used during chemotherapy treatment. The exercise prescription linearly progressed in both intensity and duration regardless of timing of chemotherapy infusions. In EXIT, a periodized aerobic exercise prescription was used during or post-chemotherapy. This is an example of a prescription for individuals on a 3-week cycle chemotherapy protocol. For participants engaging in exercise while undergoing taxane chemotherapy the planned decrease in aerobic exercise intensity aligned with the week following each chemotherapy infusion.

Figure 3: Cyclical variations in patient-reported fatigue, rating of perceived exertion (RPE), heart rate and VO2 (both absolute and relative) response to exercise (60 watts on upright cycle ergometer) and resting heart rate.
Figure 1
Figure 2

(A) Study Designs

EXIT
Baseline Assessment → Randomization → Start taxane chemotherapy → Immediate exercise “Chemo-periodized” exercise prescription → Delayed exercise Periodized exercise prescription → End of taxane chemotherapy

NExT
Baseline Assessment → Start taxane chemotherapy → Exercise Standard linear exercise prescription → End of taxane chemotherapy → Continued exercise post-chemotherapy (data not shown)

(B) Exercise Prescriptions

Intensity (%) vs. Time (wk) for each cycle:
- Cycle 1: 50% intensity, 20 min duration
- Cycle 2: 60% intensity, 30 min duration
- Cycle 3: 70% intensity, 40 min duration
- Cycle 4: 80% intensity, 50 min duration

Intensity (%) vs. Time (wk) for intensity:
- Cycle 1: Linear increase from 50% to 80%
- Cycle 2: Steady-state exercise test
- Cycle 3: Flat line at 80%
- Cycle 4: Flat line at 80%

Patient-reported fatigue

Note: Figures show a graphical representation of study designs and exercise prescriptions. The graphs depict intensity and time for different cycles, indicating variations in exercise protocols over the course of a clinical trial.
Figure 3
Table 1: EXIT and NExT participant baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy-periodized prescription (n=12)</th>
<th>Regular periodized prescription (n=15)</th>
<th>Standard linear prescription (n=51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) (mean±SD)</td>
<td>51.0±8.1</td>
<td>49.5±11.1</td>
<td>51.9±11.7</td>
</tr>
<tr>
<td>Body mass index (kg/m²) (mean±SD)</td>
<td>25.2±5.7</td>
<td>26.1±5.8</td>
<td>24.5±5.3</td>
</tr>
<tr>
<td>Marital status (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Common-law</td>
<td>10 (83%)</td>
<td>14 (93%)</td>
<td>35 (69%)</td>
</tr>
<tr>
<td>Single/widowed/divorced</td>
<td>2 (17%)</td>
<td>1 (7%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td>Ethnicity (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>8 (67%)</td>
<td>10 (67%)</td>
<td>34 (67%)</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (33%)</td>
<td>4 (31%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Education (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than a Bachelor’s degree</td>
<td>5 (42%)</td>
<td>6 (40%)</td>
<td>22 (43%)</td>
</tr>
<tr>
<td>Bachelor’s degree or higher</td>
<td>7 (58%)</td>
<td>8 (53%)</td>
<td>29 (57%)</td>
</tr>
<tr>
<td>Prefer not to answer</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Breast cancer stage (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>1 (8%)</td>
<td>4 (27%)</td>
<td>16 (31%)</td>
</tr>
<tr>
<td>II</td>
<td>4 (33%)</td>
<td>9 (60%)</td>
<td>30 (59%)</td>
</tr>
<tr>
<td>III</td>
<td>5 (42%)</td>
<td>2 (13%)</td>
<td>5 (10%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (17%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Chemotherapy protocol (n (%))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paclitaxel (with prior doxorubicin and cyclophosphamide)</td>
<td>8 (67%)</td>
<td>12 (80%)</td>
<td>30 (59%)</td>
</tr>
<tr>
<td>Docetaxel + cyclophosphamide</td>
<td>4 (33%)</td>
<td>3 (20%)</td>
<td>21 (41%)</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>4 (33%)</td>
<td>5 (33%)</td>
<td>20 (39%)</td>
</tr>
</tbody>
</table>
Table 2: Comparison of adherence and barriers to attendance between a standard linear prescription during chemotherapy, a chemotherapy-periodized prescription and a regular periodized prescription (taking place post-chemotherapy)

<table>
<thead>
<tr>
<th>Adherence</th>
<th>Standard linear prescription (n=51)</th>
<th>Chemotherapy-periodized prescription (n=12)</th>
<th>p-value, standard linear vs chemotherapy-periodized</th>
<th>Regular periodized prescription (n=14)</th>
<th>p-value, chemotherapy-periodized vs regular periodized</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Frequency</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>63±25</td>
<td>78±23</td>
<td><strong>0.05</strong></td>
<td>81±20</td>
<td>0.79</td>
</tr>
<tr>
<td>Chemo wk</td>
<td>57±30</td>
<td>77±28</td>
<td><strong>0.04</strong></td>
<td>83±20</td>
<td>0.56</td>
</tr>
<tr>
<td>Non-chemo/ recovery wk</td>
<td>65±26</td>
<td>79±21</td>
<td>0.09</td>
<td>79±21</td>
<td>0.93</td>
</tr>
<tr>
<td>p-value, chemo vs non-chemo wk</td>
<td><strong>0.01</strong></td>
<td>0.83</td>
<td></td>
<td>0.60</td>
<td></td>
</tr>
<tr>
<td><strong>Aerobic intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>69±32</td>
<td>77±30</td>
<td>0.34</td>
<td>81±17</td>
<td>0.69</td>
</tr>
<tr>
<td>Chemo wk</td>
<td>68±32</td>
<td>92±12</td>
<td><strong>&lt;0.01</strong></td>
<td>88±13</td>
<td>0.39</td>
</tr>
<tr>
<td>Non-chemo/ recovery wk</td>
<td>70±27</td>
<td>73±32</td>
<td>0.73</td>
<td>75±21</td>
<td>0.81</td>
</tr>
<tr>
<td>p-value, chemo vs non-chemo wk</td>
<td>0.86</td>
<td><strong>0.05</strong></td>
<td></td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td><strong>Aerobic duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>78±28</td>
<td>78±24</td>
<td>0.94</td>
<td>81±21</td>
<td>0.79</td>
</tr>
<tr>
<td>Chemotherapy wk</td>
<td>81±31</td>
<td>77±30</td>
<td>0.72</td>
<td>83±20</td>
<td>0.56</td>
</tr>
<tr>
<td>Non-chemo/ recovery wk</td>
<td>76±32</td>
<td>79±22</td>
<td>0.69</td>
<td>79±22</td>
<td>0.93</td>
</tr>
<tr>
<td>p-value, chemo vs non-chemo wk</td>
<td>0.25</td>
<td>0.59</td>
<td></td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td><strong>Resistance exercises, sets, weight</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>50±37</td>
<td>78±37</td>
<td><strong>0.03</strong></td>
<td>93±6</td>
<td>0.19</td>
</tr>
<tr>
<td>Chemo wk</td>
<td>50±40</td>
<td>86±29</td>
<td><strong>0.01</strong></td>
<td>90±8</td>
<td>0.73</td>
</tr>
<tr>
<td>Non-chemo/ recovery wk</td>
<td>51±39</td>
<td>78±37</td>
<td><strong>0.03</strong></td>
<td>95±8</td>
<td>0.16</td>
</tr>
<tr>
<td>p-value, chemo vs non-chemo wk</td>
<td>0.59</td>
<td>0.75</td>
<td></td>
<td><strong>0.04</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Barriers to attendance</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment symptoms</td>
<td>29%</td>
<td>52%</td>
<td><strong>&lt;0.01</strong></td>
<td>1%</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Conflicting appointment</td>
<td>20%</td>
<td>18%</td>
<td>0.80</td>
<td>13%</td>
<td>0.41</td>
</tr>
<tr>
<td>Vacation</td>
<td>19%</td>
<td>2%</td>
<td><strong>&lt;0.01</strong></td>
<td>20%</td>
<td><strong>&lt;0.01</strong></td>
</tr>
<tr>
<td>Cold/flu</td>
<td>15%</td>
<td>17%</td>
<td>0.70</td>
<td>4%</td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Work</td>
<td>5%</td>
<td>0%</td>
<td>0.10</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>Family obligations</td>
<td>5%</td>
<td>3%</td>
<td>1.00</td>
<td>7%</td>
<td>0.45</td>
</tr>
<tr>
<td>Non-cancer-treatment-related injury</td>
<td>0%</td>
<td>0%</td>
<td>-</td>
<td>43%</td>
<td><strong>&lt;0.01</strong></td>
</tr>
</tbody>
</table>

Abbreviations: chemo = chemotherapy; wk = week;