Hemoglobin and Aerobic Fitness Changes with Supervised Exercise Training in Breast Cancer Patients Receiving Chemotherapy

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Abstract

Background: Aerobic exercise training (AET) is known to increase RBC production; however, this has not been evaluated in breast cancer patients undergoing adjuvant chemotherapy. The purpose of this study was to examine the changes in hemoglobin (Hb) levels in the Supervised Trial of Aerobic versus Resistance Training (START) and to determine its association with changes in VO₂peak.

Methods: Two hundred and forty-two breast cancer patients initiating chemotherapy were randomized to usual care (n = 82), resistance exercise (RET, n = 82), or AET (n = 78) groups for the duration of their chemotherapy (median, 17 weeks). Supervised exercise was thrice weekly based on standard AET and RET prescriptions. Aerobic fitness (VO₂peak) and Hb concentration were measured at baseline and end of chemotherapy.

Results: Regardless of the exercise group, Hb declined over the course of chemotherapy (13.4 ± 10.0 to 11.8 ± 11.5 g/dL, P < 0.001). Both AET and RET groups had significant, moderate correlations between the change in VO₂peak and Hb (AET: r = 0.49, P < 0.001; RET: r = 0.39, P = 0.001).

Conclusion: The results indicate that regular exercise does not protect against the decline in Hb associated with chemotherapy in breast cancer patients, but resulted in a stronger association between Hb and VO₂peak.

Impact: Even with the chemotherapy-induced decline in Hb, breast cancer patients can maintain their aerobic capacity by participating in regular aerobic exercise. Further studies are required to determine safe intensity levels that may stimulate the maintenance of Hb levels in breast cancer patients. Cancer Epidemiol Biomarkers Prev; 19(11): 2826–32. ©2010 AACR.

Introduction

Breast cancer patients undergoing adjuvant therapy commonly suffer from a decline in hemoglobin (Hb) concentration, which in cancer patients has been related to higher rates of fatigue and depression, combined with a deterioration in physical functioning (1), quality of life (2), and survival (3). Kirshner and colleagues (4) reported a ~40% increase in the incidence of moderate to severe anemia (Hb levels <10 g/dl) in stage II and III breast cancer patients undergoing adjuvant doxorubicin and cyclophosphamide chemotherapy. Treatment of severe anemia may require erythrocyte transfusion, but this carries the risk of transfusion reactions and infectious disease transmission. Erythropoietic supportive agents (ESA) are only moderately effective and their use in cancer-related anemia increases thromboembolic complications and hypertension, and has been associated with adverse effects on survival (5-7). Furthermore, recent evidence suggesting tumor-stimulating effects of ESAs are of particular concern in the curative-intent setting of adjuvant breast cancer chemotherapy (8).

Exercise could be an appropriate nonpharmacologic intervention to counteract the decline in Hb observed in many breast cancer patients undergoing chemotherapy. Aerobic exercise training (AET) is associated with improved hemorheology (see refs. 9-11 for in-depth reviews) and can increase blood volume through an increase in plasma volume and RBC mass (12). Few studies have evaluated the effect of exercise training on Hb in breast cancer patients undergoing adjuvant...
Exercise during Chemotherapy

Previous studies have reported positive changes in Hb with exercise in cancer patients, but the samples were small and clinically heterogeneous, with brief interventions of 6 to 9 weeks, which occurred after chemotherapy (13, 14).

We recently evaluated the relative merits of AET and resistance exercise training (RET) in moderating these negative side effects caused by chemotherapy in the Supervised Trial of Aerobic versus Resistance Training (START; ref. 15). The START trial was a randomized controlled trial designed to compare the effects of AET and RET to usual care (UC) in breast cancer patients receiving adjuvant chemotherapy. The results of this study showed that AET was superior to UC for improving self-esteem, preserving aerobic fitness (VO2peak), and maintaining body fat levels, whereas RET was superior to UC for improving self-esteem, increasing muscular strength, adding lean body mass, and facilitating completion of chemotherapy treatment (16). All other outcomes, including the primary endpoint of quality of life, favored the exercise groups over UC but did not reach statistical significance (16).

Although aerobic fitness was preserved in the AET group, it did not improve despite the AET stimulus. One possible explanation for this finding is that changes in peripheral and central adaptations with AET were offset by declines in Hb. We have not evaluated the effect of exercise training during adjuvant chemotherapy on Hb levels. Thus, the purpose of the present study was to examine the changes in Hb concentration with exercise training in breast cancer patients undergoing adjuvant chemotherapy and to determine associations with change in VO2peak. We hypothesized that the UC and RET groups would show a decline in Hb over the course of chemotherapy, whereas the AET group would maintain or increase Hb.

Materials and Methods

Setting and participants

Detailed methods of the START trial have been reported elsewhere (16), but we have included a brief summary. Participants were recruited from the British Columbia Cancer Agency (Vancouver, British Columbia, Canada), Cross Cancer Institute (Edmonton, Alberta, Canada), and the Ottawa Hospital Integrated Cancer Program (Ottawa, Ontario, Canada). The trial received ethical approval from all three centers and written informed consent from all participants. English or French speaking, nonpregnant women, ≥18 years old, with stage I to IIIA breast cancer that were initiating first-line adjuvant chemotherapy were eligible to participate. Women were excluded if they had incomplete axillary surgery, transabdominal rectus abdominus muscle reconstructive surgery, uncontrolled hypertension, cardiac illness, and psychiatric illness, or were otherwise not approved for participation by their oncologist.

Design and procedures

The study was a prospective, three-armed, randomized controlled trial. Eligible participants were identified by their treating oncologist before chemotherapy. Interested participants completed a questionnaire, physical fitness test, and dual X-ray absorptiometry scan (added after the first 23 participants were randomized) and had blood drawn for the determination of Hb. Charts were reviewed for use of ESAs and blood transfusions in all participants.

Randomization

Participants were stratified by center and chemotherapy protocol (taxane versus nontaxane based) and randomly assigned to either AET, RET, or UC in a 1:1:1 ratio using a computer-generated program. The allocation sequence was generated in Edmonton and concealed from the project directors at each site.

Exercise training interventions

Participants exercised three times a week for the duration of their chemotherapy, beginning 1 to 2 weeks after starting chemotherapy and ending 3 weeks after chemotherapy. The AET group exercised on a cycle ergometer, treadmill, or elliptic trainer, beginning at heart rate that elicited 60% of their VO2peak for the first 6 weeks (17). During weeks 7 to 12, women exercised at 70% of their VO2peak progressing to 80% beyond week 12. Initial duration was 15 minutes and increased by 5 minutes every 3 weeks until 45 minutes was attained and then maintained. The RET group did two sets of 8 to 12 repetitions of nine different exercises at 60% to 70% of their estimated 1 repetition maximum (18) with prespecified weight progression. Individuals randomized into the UC group were asked not to perform aerobic or anaerobic exercises more than 15 minutes per week.

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Table 1. Physical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Overall (N = 242)</th>
<th>UC (n = 82)</th>
<th>RET (n = 82)</th>
<th>AET (n = 78)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y), mean (range)</td>
<td>49.2 (25-78)</td>
<td>49.0 (26-78)</td>
<td>49.5 (25-76)</td>
<td>49.0 (30-75)</td>
<td>0.946</td>
</tr>
<tr>
<td>Weight (kg), mean (SD)</td>
<td>70.6 (14.3)</td>
<td>72.6 (15.2)</td>
<td>69.7 (14.4)</td>
<td>69.4 (13.3)</td>
<td>0.282</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>26.6 (5.5)</td>
<td>27.1 (5.4)</td>
<td>26.1 (5.5)</td>
<td>26.7 (5.6)</td>
<td>0.518</td>
</tr>
</tbody>
</table>

NOTE: Adapted from Courneya et al. (16).
Abbreviation: BMI, body mass index.
initiate an exercise program and were offered a 1-month exercise program after post-intervention assessments.

Assessment of primary and secondary endpoints

Aerobic fitness was assessed at baseline and after intervention. Aerobic fitness was evaluated using a maximal incremental exercise protocol on a treadmill (19). Hb was determined from resting blood samples drawn at the initiation and after the completion of chemotherapy. Sampling occurred approximately within 2 weeks of the maximal incremental exercise test.

Statistical analyses and sample size calculation

The sample size calculation was originally based on a change in the FACT-An score (16). Specifically, with 80 participants per group, our trial had 0.80 power to detect a difference in change scores of 7 points (SD, 16) on the FACT-An (20) with a loss to follow-up of 10%, a two-tailed α = 0.05, and no adjustment for multiple testing. Mixed-model repeated measures analysis was used to compare the differences in group changes over time. To detect any main effects of chemotherapy regimen (non-taxane versus taxane based) between groups on percent change in VO2peak and Hb, a 2 × 3 between-group analysis was done. If effects were significant, a follow-up 1 × 3 between-group analysis was done.

Results

Detailed flow of participants through the trial has been reported elsewhere (16). Briefly, we recruited 242 of 736 (33%) eligible participants and obtained follow-up data on >90% of participants for each outcome. Physical characteristics are contained in Table 1. Further details about disease stage, surgical treatment, and chemotherapy protocols have been previously reported (16). The groups were balanced on all variables at baseline, including VO2peak and Hb. The median length of the exercise intervention was 17 weeks (95% confidence interval, 9-24), and adherence was 72.0% and 68.2% in the AET and RET groups, respectively (P = 0.41; ref. 21). No participant received erythrocyte transfusion during the course of the study. One patient is suspected to have been administered an ESA.

Changes in objectively measured outcomes

Analysis of pretest scores found no significant differences between groups for VO2peak (P = 0.758) and Hb (P = 0.254). Pre- and post–VO2peak and Hb values are presented in Table 2. As previously reported, the AET group maintained VO2peak (P = 0.80), whereas both UC and RET showed a significant decline (P ≤ 0.001 and P = 0.002, respectively; ref. 16). All groups showed a similar and significant decline in Hb from pre- to post-test of ∼14% (AET: 13.4 ± 1.2 g/dL to 11.9 ± 1.3 g/dL, P < 0.001; UC: 13.3 ± 1.1 g/dL to 11.7 ± 1.1 g/dL, P < 0.001; RET: 13.6 ± 0.7 g/dL to 11.0 ± 1.18 g/dL, P < 0.001). Of 242 subjects, 102 subjects (33 UC, 38 RET, 31 AET) completed chemotherapy with Hb levels above 12 g/dL, 76 subjects (24 UC, 25 RET, and 27 AET) completed chemotherapy with Hb between 11 and 12 g/dL, whereas 64 subjects (25 UC, 19 RET, and 20 AET) completed chemotherapy with Hb <11 g/dL.

The between-group difference in percent change of VO2peak from pre- to post-test varied by chemotherapy regimen (P = 0.012). Specifically, breast cancer patients receiving nontaxane-based chemotherapies maintained VO2peak in the AET group (P = 0.613), whereas both the UC and RET groups showed a significant decline (P = 0.002 and P = 0.009, respectively). Breast cancer patients receiving taxane-based chemotherapies (either docetaxel or paclitaxel) maintained VO2peak in AET and RET groups (P = 0.797 and P = 0.113, respectively), whereas the UC group showed a significant decline (P = 0.039). The decline in Hb was similar between chemotherapy regimens (P = 0.34).

Both the AET and RET groups had significant, moderate correlations (AET: r = 0.49, P < 0.001; RET: r = 0.31, P = 0.007) between the percentage change in VO2peak and Hb from pre- to post-test (Fig. 1). UC had a nonsignificant, weak correlation between VO2peak and Hb (r = 0.17, P = 0.16).

As the AET group did not significantly improve either VO2peak or Hb, we did an ad hoc analysis to determine if failure to meet the prescribed exercise prescription could account for the findings. Overall, subjects in the AET group met the prescribed duration and intensity prescription 69 ± 30.0% and 63 ± 29.7%, respectively, of the time. For this analysis, we arbitrarily divided...
the AET group into two groups: those subjects who followed the prescribed duration and intensity prescriptions ≥80% of the time and those subjects who did not satisfy this criterion. Although not significantly different, subjects in the AET group that met the intensity prescription >80% of the time had a 2.0% (SE, 3.5) increase in VO$_2$peak whereas those AET subjects that did not follow the intensity prescription had a 3.1% (SE, 2.2) decrease in VO$_2$peak ($P = 0.195$). Similar results were seen for duration. There was no substantive affects of adherence on Hb. Both groups had a similar decline in Hb of ∼13% ($P = 0.767$).

Discussion

This study examined the relationship between the decline in Hb and the changes in aerobic capacity in female breast cancer patients, who participated in an exercise intervention during chemotherapy. Contrary to our hypothesis, all breast cancer patients, regardless of group assignment, showed a significant decline in Hb over the course of chemotherapy. However, subjects in the aerobic group, even with a chemotherapy-induced drop in Hb, maintained their aerobic fitness, and for those women who attained their intensity/duration prescriptions >80% of the time, a slight, nonsignificant rise in VO$_2$ occurred.

Cancer-related anemia can produce an escalating series of side effects that can impair quality of life (2, 22). Specifically, breast cancer patients have shown a significant relationship between anemia and decreased functional capacity (23), quality of life, and survival (3, 24, 25). The relationship between chemotherapy-induced anemia and aerobic capacity in breast cancer patients is important. The correlation of the drop in Hb with the percent change in VO$_2$ found in the present study is depicted in Fig. 1. Exercise mode, length of the intervention, and adherence to the exercise prescription may have influenced the results, but further research is required to investigate the mechanisms responsible and the intensity levels, duration, or adherence that are necessary to evoke changes in Hb in this population.

In healthy individuals, who voluntarily became anemic, a decline in cardiovascular fitness occurred (26-28) such that a 14% drop in Hb caused a 10% drop in VO$_2$ (28). Such deteriorations in aerobic capacity can have a significant effect on survival: in a cohort of ∼6,000 asymptomatic women, a change in 1 MET (3.5 mL/kg/min) corresponded to a 17% difference in mortality rate (29). However, using aerobic capacity as a prognostic tool has yet to be evaluated in breast cancer patients.

In this study, Hb levels decreased equally (∼14%) between the control, resistance, and aerobic groups, suggesting that the chemotherapy-induced anemia was not prevented with our exercise training stimulus. The results of the present study are similar to those found by Dimeo et al. (1), who investigated Hb with endurance training in patients with hematologic malignancies during chemotherapy. These authors showed that the patients were able to maintain physical performance, as determined by a submaximal standard stress test, despite a significant decrease in mean Hb.

Raising Hb through exercise is hypothesized to occur following the increase in plasma volume associated with exercise training. This rise creates a relative drop in the Hb and oxygen concentration in arterial blood, consequently stimulating erythropoiesis. It may be argued that (a) neither exercise protocol was sufficient to prevent a decline in Hb, as there was no significant increase in aerobic capacity, and (b) the myelosuppressive effect of the systemic therapy outweighed the potential exercise stimulus on the erythropoietic system. This suggests that our chosen exercise duration was too short, or the intensity may have been too low to supersede the suppressive effects of the concurrent chemotherapy, thus preventing the maintenance of Hb. However, 7 weeks of moderate intensity exercise has been shown to prevent the decline in Hb in breast cancer patients undergoing radiation therapy (14) and to improve Hb in cancer patients with severe anemia (13).

This study reveals that even with mild to moderate anemia, breast cancer patients who take part in regular, low- to moderate-intensity aerobic exercise are able to maintain their VO$_2$peak. Maintaining aerobic capacity, even with a chemo-induced decline in Hb, validates the benefits of implementing an exercise intervention program to counteract the many side effects of breast cancer treatments. We can speculate that the maintenance of aerobic capacity may be explained by peripheral adaptations, rather than central changes in the cardiovascular system. The exercise intervention may have improved red cell deformability and lowered blood viscosity, thus enhancing oxygen transport (30). In addition, adaptations may have occurred at the mitochondrial level, with changes in the number, size, or mitochondrial efficiency that compensated for the decrease in Hb. It has been reported that non-Hb effects on physical work capacity can occur with training (31), such that an increase in work capacity can occur that is not matched by increases in Hb (32). The moderate correlations depicted in Fig. 1 may be explained by these peripheral adaptations. Improvements in tissue oxidative capacity may have allowed the women in this study to maintain their aerobic capacity, thus maintaining the capability to do day-to-day chores during chemotherapy.

A limitation of this study is that the treatment of anemia with erythropoietin during the time course of the study was not properly documented in one individual. However, this was a large, randomized controlled trial; thus, we expect the effect to be minimal.

In this study, regular exercise did not prevent the decline in Hb associated with adjuvant chemotherapy in breast cancer patients. However, even with the chemotherapy-induced decline in Hb, breast cancer patients were able to maintain their aerobic capacity by participating in a supervised exercise program. Further
Figure 1. Correlations between the percent change in Hb and the percent change in VO$_2$ during chemotherapy treatment in the (A) controls, (B) resistance group, and (C) aerobic group.
studies are required to determine safe intensity levels that may stimulate the maintenance of Hb in breast cancer patients.

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interest were disclosed.

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