

Effects of Aerobic Exercise Training in Anemic Cancer Patients Receiving Darbepoetin Alfa: A Randomized Controlled Trial

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ABSTRACT

Background. Anemia in patients with solid tumors is a common problem that is associated with impaired exercise capacity, increased fatigue, and lower quality of life (QoL). Erythropoiesis-stimulating agents (ESAs) have been shown to improve these outcomes; however, it is unknown if additional benefits can be achieved with aerobic exercise training.

Methods. We conducted a single-center, prospective, randomized, controlled trial in 55 mild-to-moderately anemic patients with solid tumors. Patients were randomized to either darbepoetin alfa alone (DAL, $n = 29$) or darbepoetin alfa plus aerobic exercise training (DEX; $n = 26$). The DEX group performed aerobic exercise training three times per week at 60%–100% of baseline exercise capacity for 12 weeks. The primary endpoint was QoL assessed by the Functional Assessment of Cancer Therapy–Anemia scale. Secondary endpoints were fatigue, cardio-

respiratory fitness (VO_{2peak}), hemoglobin (Hb) response, and darbepoetin alfa dosing.

Results. Intention-to-treat analyses indicated significant improvements in QoL and fatigue in both groups over time but there were no between-group differences. The DEX group had a significantly greater VO_{2peak} than the DAL group (mean group difference, +3.0 ml/kg per minute; 95% confidence interval, 1.2–4.7; $p = .001$) and there were borderline significant differences in favor of the DEX group for Hb response and darbepoetin alfa dosing.

Conclusions. Aerobic exercise training did not improve QoL or fatigue beyond the established benefits of DAL but it did result in favorable improvements in exercise capacity and a more rapid Hb response with lower dosing requirements. Our results may be useful to clinicians despite the more recent restrictions on the indications for ESAs. *The Oncologist* 2008;13:1012–1020

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INTRODUCTION

Anemia in patients with solid tumors is a common problem that is associated with impaired exercise capacity, increased fatigue, and lower quality of life (QoL) [1]. Erythropoiesis-stimulating agents (ESAs) can improve these outcomes and reduce the need for blood transfusions [2–5], although they have not been shown to improve overall survival [6–8]. Epoetin alfa (Eprex®; Ortho Biotech, Toronto, Canada) and darbepoetin alfa (Aranesp®; Amgen Inc., Thousand Oaks, CA) are approved in Canada for the treatment of anemia in nonmyeloid malignancies where anemia is a result of the concomitant administration of chemotherapy. Darbepoetin alfa is a recombinant erythropoietin with a longer half-life than epoetin alfa [9], which allows for less frequent dosing with similar efficacy in terms of hemoglobin (Hb) and QoL responses [4, 10, 11].

Aerobic exercise training has been shown to improve cardiorespiratory fitness, fatigue, and some aspects of QoL in nonanemic cancer patients [12–15], but has not been studied in anemic cancer patients. ESAs increase Hb but they do not induce central (i.e., cardiac output) or peripheral (i.e., Hb extraction and use) adaptations [16, 17]. Exercise training can improve these parameters with no expected change in Hb levels. Consequently, ESAs and exercise training may have complementary pathways toward improving cardiovascular fitness, fatigue, and QoL. No study to date, however, has examined this issue.

Here, we report results from the Exercise Training and Anemia (EXTRA) trial comparing the effects of darbepoetin alfa alone (DAL) with those of darbepoetin alfa plus aerobic exercise training (DEX) on QoL, fatigue, cardiorespiratory fitness, Hb response, and drug dosing requirement in mild-to-moderately anemic cancer patients. We hypothesized that DEX would improve QoL, fatigue, and cardiorespiratory fitness beyond the benefits of DAL. An exploratory aim was to examine the effects of exercise on Hb response and drug requirement.

METHODS

Setting and Participants

Participants were recruited from the Cross Cancer Institute (CCI), Edmonton, Canada. The study received ethical approval from the Alberta Cancer Board and the University of Alberta. Eligible patients had a histologically confirmed nonmyeloid cancer diagnosis, an Hb level of 80–110 g/l, an Eastern Cooperative Oncology Group performance status score of 0–2, completed definitive surgery, an expected survival duration ≥ 3 months, and were English speaking and ≥ 18 years of age. Patients were excluded from the trial

if they had iron deficiency (ferritin $< 12 \mu\text{g/l}$), had received an ESA within 4 weeks of randomization, or had uncontrolled hypertension, cardiac abnormalities, a psychiatric illness, a known hematologic disorder causing anemia, substantial lung, pleural, or pericardial disease, preexisting bone metastases at high risk for fracture, or contraindications to maximal exercise testing.

Design and Procedures

A single-center, prospective, two-armed, randomized, controlled trial was performed. Potential eligible participants were identified by a central screening of patient Hb levels at the CCI. After obtaining primary oncologist approval, potential patients were approached by the trial research nurse and, if interested, provided written informed consent. Screening and study outcomes included a CBC, serum ferritin, total iron binding capacity, physical examination, and medical history including prior ESA use and blood transfusions, a self-administered QoL questionnaire, and a maximal aerobic exercise test.

Randomization and Blinding

Participants were stratified by current chemotherapy (yes versus no) and randomly assigned to either DAL or DEX in a 1:1 ratio using a computer-generated program. The allocation sequence was concealed from the project director who assigned participants to groups. It was not possible to blind participants or exercise trainers to group assignment. Oncologists making decisions about darbepoetin alfa administration were blinded to group assignment.

Darbepoetin Alfa Therapy

All participants were evaluated for darbepoetin alfa treatment at a dose of $4.5 \mu\text{g/kg}$ on weeks 1, 2, 3, 4, 5, 8, and 11. The Hb level was determined prior to each planned darbepoetin administration and darbepoetin was withheld if the patient's Hb concentration increased to $\geq 140 \text{ g/l}$ for men or $\geq 130 \text{ g/l}$ for women. Darbepoetin was reinstated at 50% of the previous dose when the Hb level returned to $< 120 \text{ g/l}$. Participants received oral iron supplementation when baseline ferritin levels were $< 50 \mu\text{g/l}$.

Aerobic Exercise Training Intervention

The exercise training program was individually tailored to each participant and aimed at improving cardiorespiratory fitness. All exercise training sessions were supervised by exercise physiologists and consisted of three cycle ergometry sessions per week for 12 weeks at 60%–100% of baseline peak power output. Patients in the DAL group were

asked not to initiate a structured exercise program during the intervention period.

Timing and Assessment of Study Endpoints

All study outcomes were assessed at baseline (within 10 days prior to starting darbepoetin alfa) and postintervention (1–2 weeks after the 12-week intervention period). QoL and fatigue were assessed using the Functional Assessment of Cancer Therapy–Anemia (FACT-An) scale [18]. To determine VO_{2peak} , a physician-supervised maximal exercise test with 12-lead electrocardiogram monitoring (Mac® 5000, GE Healthcare, Milwaukee, Wisconsin) was performed. The specific protocol for this test has previously been reported in detail [19]. In brief, the test was performed on an electronically braked cycle ergometer (Ergoselect 100; Ergoline, Bitz, Germany) with breath-by-breath expired gas analysis continuously measured on a calibrated metabolic measurement system (CPX/D system; Medgraphics, St. Paul, MN). Workloads were increased 5–20 watts/minute until volitional exhaustion or symptom limitation. All metabolic data were averaged over 30-second periods with the highest 30-second VO_2 recorded as the VO_{2peak} . The ventilatory threshold (VT) was determined using the ventilatory equivalent method [20]. The Hb level was assessed at baseline (week 0) and weeks 1, 2, 3, 4, 7, and 10, and postintervention (week 13) by an automated CBC.

Assessment of Covariates, Exercise Adherence, and Adverse Events

Demographic data were collected by self-report and medical data were abstracted from clinical records. Exercise adherence and exercise-related adverse events were monitored by fitness center staff. Darbepoetin alfa-related adverse events were monitored by the study research nurse during each visit. Nonprotocol exercise was assessed in both groups by self-report [21].

Statistical Analyses

Our original sample size goal was to have 100 evaluable participants (50 in each group) based on randomizing 115 participants and allowing for a 10%–15% loss to follow-up. With 50 participants per group, we would have had a 0.80 power to detect a change score difference of 12 points (standard deviation [SD], 24) on the FACT-An using a two-tailed $\alpha = 0.05$. Following accrual difficulties, the protocol was modified to randomize 55 participants to obtain 50 evaluable participants (25 per group), which allowed for the detection of a 19-point (SD, 24) change on the FACT-An. Study endpoints were analyzed using independent *t*-tests to compare change scores be-

tween groups from baseline to postintervention according to intention-to-treat principles using the last-observation-carried-forward method. The DAL group score was subtracted from the DEX group score. All analyses were repeated adjusting for the baseline value of the outcome, age, sex, marital status, education, primary tumor type (breast versus other), metastatic disease (yes versus no), current chemotherapy (yes versus no), and prior blood transfusion (yes versus no). The Hb level and drug dosing were analyzed using unadjusted and adjusted repeated measures analyses of variance (RM-ANOVA). We also conducted a Kaplan–Meier analysis on the time to Hb response, defined as an increase in Hb of ≥ 20 g/l over baseline.

RESULTS

Recruitment began July 2003 and ended September 2006. The study flow is presented in Figure 1. We recruited 55 of 224 (24.4%) eligible participants (Fig. 1). QoL/fatigue follow-up data were obtained on 54 of 55 (98.2%) participants, cardiorespiratory fitness data were obtained on 51 of 55 (92.7%) participants, and Hb data were obtained on 377 of 385 (97.9%) visits.

Baseline characteristics are provided in Table 1 and were well balanced between groups. The DAL and DEX groups attended 379 of 385 (98.4%) drug evaluation visits. The DEX group attended 84.2% (30.3/36) of their scheduled exercise sessions and achieved the prescribed exercise duration and intensity in 94.7% (28.7/30.3) and 94.1% (28.5/30.3) of the sessions, respectively. During the intervention period, the DAL group reported 32 ± 80 minutes of nonprotocol-related moderate-to-strenuous exercise per week (i.e., at least brisk walking) compared with 63 ± 114 minutes per week for the DEX group ($p = .245$). There were no exercise-related serious adverse events and no participant experienced an adverse event related to darbepoetin alfa therapy.

Changes in Quality of Life and Fatigue

Table 2 presents the QoL and fatigue endpoints. There were no between-group differences, but Table 2 demonstrates that both groups significantly improved QoL and fatigue over time. Adjustment for covariates did not alter these findings (Table 2).

Changes in Cardiorespiratory Fitness

Table 3 presents the cardiorespiratory fitness endpoints. The VO_{2peak} was significantly greater in the DEX group than in the DAL group (mean group difference, +3.0; 95% confidence interval [CI], 1.2–4.7; $p = .001$). Similar findings were observed for peak watts ($p = .028$) and VT ($p =$

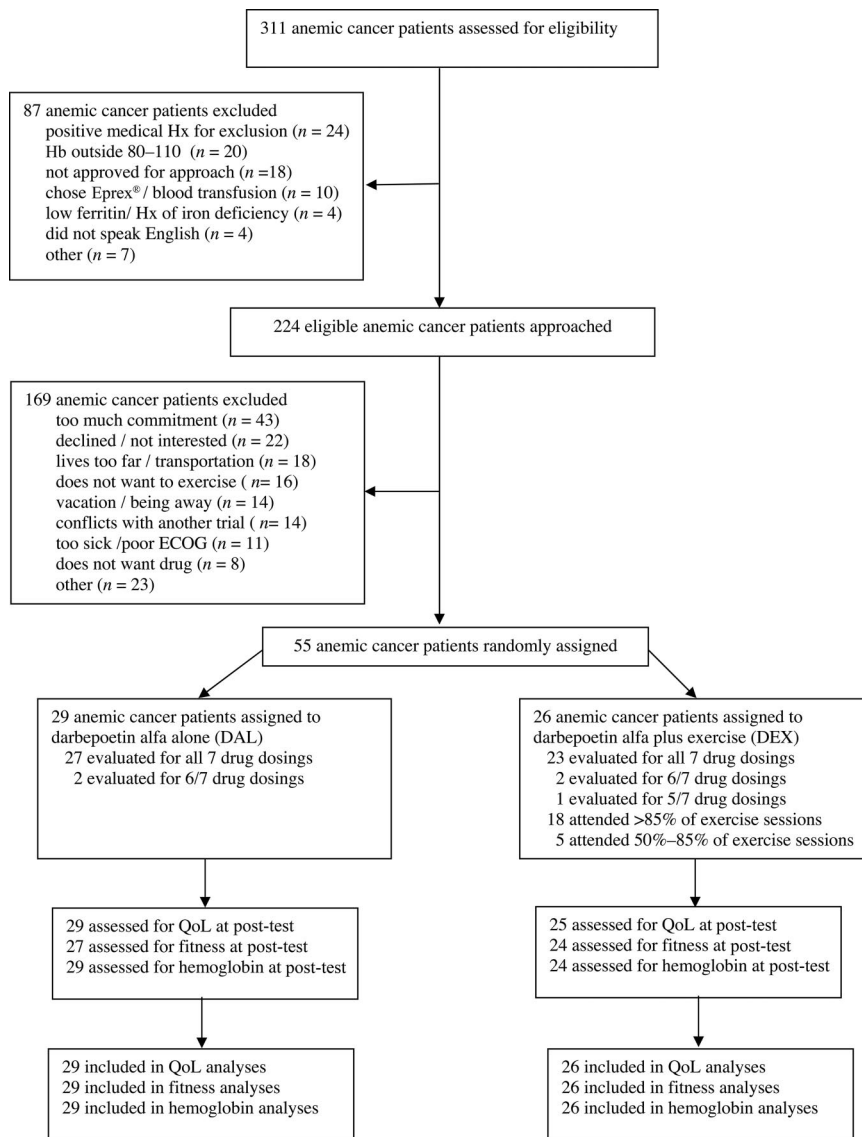


Figure 1. Flow of participants through the trial. Abbreviations: ECOG, Eastern Cooperative Oncology Group; Hb, hemoglobin; Hx, history; QoL, quality of life.

.001). Adjustment for covariates did not alter these findings (Table 3).

Hb Response and Drug Dosing Requirement

The mean Hb concentration improved from 101.2 g/l at baseline to 123.4 g/l postintervention in the DAL group and from 103.9 g/l at baseline to 120.6 g/l postintervention in the DEX group (Table 4). Postintervention, 15 of 29 (51.7%) participants in the DAL group had achieved an Hb response (a 20-g/l increase in Hb concentration) compared with 19 of 26 (73.1%) in the DEX group ($\chi^2(1) = 2.6; p = .104$). Because of the dose titration rules employed in the study, the mean Hb after achievement of the target stabilized at approximately 120 g/l in both groups (Table 4). No participant in the trial required a transfusion during the trial treatment period.

The DEX group had a more rapid rise in Hb (Table 4; Fig. 2). RM-ANOVA yielded a borderline significant time by group interaction for Hb level (Wilks' $\lambda = 0.78$; $F(7,47) = 1.9; p = .085$). Adjustment for covariates slightly strengthened this interaction (Wilks' $\lambda = 0.72$; $F(7,38) = 2.1; p = .067$). Follow-up independent *t*-tests revealed that the DEX group had higher Hb levels at week 4 ($p = .016$) and borderline higher levels at week 7 ($p = .084$). The Kaplan–Meier analysis also indicated a borderline significant group effect for time to an Hb response of ≥ 20 g/l (generalized Wilcoxon $\chi^2(1) = 3.4; p = .065$; Fig. 3).

RM-ANOVA also showed a trend toward a significant time by group interaction for drug dosing (Wilks' $\lambda = 0.84$; $F(6,48) = 1.6; p = .181$) (Table 4), which was

Table 1. Baseline demographic and medical profile of participants overall and by group assignment

Variable	Overall (n = 55)	DAL (n = 29)	DEX (n = 26)	p-value
Demographic profile				
Age, mean (range), years	56 (25–77)	54 (25–77)	58 (40–77)	.226
Female, n (%)	45 (81.8%)	25 (86.2%)	20 (76.9%)	.373
Married, n (%)	42 (76.4%)	24 (82.8%)	18 (69.2%)	.238
Completed university, n (%)	29 (52.7%)	13 (44.8%)	16 (61.5%)	.215
Income >\$60,000/year, n (%)	24 (43.6%)	14 (48.3%)	10 (38.5%)	.464
Full/part-time employed, n (%)	14 (25.5%)	6 (20.7%)	8 (30.8%)	.392
Current exerciser, n (%)	6 (10.9%)	3 (10.3%)	3 (11.5%)	.887
Medical profile				
Weight, mean (SD), kg	70.3 (12.6)	69.5 (13.3)	71.1 (12.0)	.639
Primary breast tumor, n (%)	33 (60.0%)	18 (62.1%)	15 (57.7%)	.741
Metastatic disease, n (%)	26 (47.3%)	11 (37.9%)	15 (57.7%)	.143
Current chemotherapy, n (%)	51 (92.7%)	26 (89.7%)	25 (96.2%)	.354
Previous anthracyclines, n (%)	10 (18.2%)	5 (17.2%)	5 (19.2%)	.841
Previous trastuzumab, n (%)	4 (7.3%)	1 (3.4%)	3 (11.5%)	.249
Previous radiotherapy, n (%)	10 (18.2%)	4 (13.8%)	6 (23.1%)	.373
Prior blood transfusion, n (%)	11 (20.0%)	7 (24.1%)	4 (15.4%)	.418
Previous erythropoietic agent, n (%)	2 (3.6%)	1 (3.4%)	1 (3.8%)	.937
Current lung disease, n (%)	11 (20.0%)	5 (17.2%)	6 (23.1%)	.589
Current heart disease, n (%)	9 (16.4%)	5 (17.2%)	4 (15.3%)	.903
ECOG score 0 or 1, n (%)	52 (94.5%)	27 (93.1%)	25 (96.2%)	.619

Abbreviations: DAL, darbepoetin alfa alone; DEX, darbepoetin alfa plus exercise; ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table 2. Effects of aerobic exercise training on quality of life and fatigue (n = 55)

Variable	Baseline, M (SD)	Postintervention, M (SD)	Mean change, M (95% CI)	Unadjusted group differences in mean change, M (95% CI)	Adjusted group differences in mean change, ^a M (95% CI)
FACT-An (0–188)					
DAL (n = 29)	123.4 (24.9)	143.7 (25.8)	+20.3 (9.2 to 31.4)	−6.9 (−22.1 to 8.3); p = .363	−3.2 (−16.7 to 10.4); p = .637
DEX (n = 26)	125.0 (26.5)	138.4 (29.4)	+13.4 (2.5 to 24.2)		
Fatigue (0–52)					
DAL (n = 29)	27.5 (10.2)	36.6 (9.8)	+9.1 (4.4 to 13.8)	−1.3 (−8.0 to 5.4); p = .694	+2.1 (−2.8 to 7.1); p = .388
DEX (n = 26)	29.8 (10.9)	37.6 (9.6)	+7.8 (2.8 to 12.8)		

^aAdjusted for baseline value, age, sex, marital status, education, primary tumor type, metastatic disease, current chemotherapy, and prior blood transfusion.
Abbreviations: CI, confidence interval; DAL, darbepoetin alone; DEX, darbepoetin plus exercise; FACT-An, Functional Assessment of Cancer Therapy–Anemia; M, mean; SD, standard deviation.

slightly strengthened after adjustment for covariates (Wilks' $\lambda = 0.79$; $F(6,40) = 1.8$; $p = .124$). Follow-up independent *t*-tests revealed that the DAL group received more drug at week 4 ($p = .052$). χ^2 analysis showed that

the percentage of treatment visits not requiring a drug injection was 13.7% (25 of 182) in the DEX group compared with 7.4% (15 of 203) in the DAL group (mean difference, 6.3%; $p = .046$).

Table 3. Effects of aerobic exercise training on cardiovascular fitness endpoints (*n* = 55)

Variable	Baseline, M (SD)	Postintervention, M (SD)	Mean change, M (95% CI)	Unadjusted group differences in mean change, M (95% CI) <i>p</i>	Adjusted group differences in mean change, ^a M (95% CI) <i>p</i>
VO_{2peak}, ml/kg/min					
DAL (<i>n</i> = 29)	16.1 (4.2)	16.6 (3.9)	+0.6 (−0.3 to 1.4)	+3.0 (1.2 to 4.7); <i>p</i> = .001	+3.0 (1.1 to 5.0); <i>p</i> = .003
DEX (<i>n</i> = 26)	15.6 (3.8)	19.1 (5.3)	+3.5 (2.0 to 5.1)		
VO_{2peak}, l/min					
DAL (<i>n</i> = 29)	1.09 (.25)	1.13 (.26)	+0.04 (−0.02 to 0.10)	+0.21 (0.08 to 0.34); <i>p</i> = .001	+0.22 (0.08 to 0.37); <i>p</i> = .004
DEX (<i>n</i> = 26)	1.08 (.26)	1.33 (.39)	+0.25 (0.13 to 0.37)		
Peak workload (watts)					
DAL (<i>n</i> = 29)	80.3 (26.1)	82.8 (26.9)	+2.4 (−3.8 to 8.7)	+11.4 (1.3 to 21.6); <i>p</i> = .028	+13.3 (1.8 to 24.7); <i>p</i> = .024
DEX (<i>n</i> = 26)	81.3 (23.1)	95.2 (34.0)	+13.8 (5.3 to 22.4)		
Ventilatory threshold, l/min					
DAL (<i>n</i> = 29)	0.61 (.15)	0.62 (0.13)	+0.01 (−0.02 to 0.04)	+0.13 (0.06 to 0.21); <i>p</i> = .001	+0.15 (0.07 to 0.23); <i>p</i> < .001
DEX (<i>n</i> = 26)	0.65 (.14)	0.79 (0.17)	+0.14 (−0.07 to 0.21)		

^aAdjusted for baseline value, age, sex, marital status, education, primary tumor type, metastatic disease, current chemotherapy, and prior blood transfusion.
Abbreviations: CI, confidence interval; DAL, darbepoetin alone; DEX, darbepoetin plus exercise; M, mean; SD, standard deviation; VO_{2peak}, peak volume of oxygen consumed.

Table 4. Effects of aerobic exercise training on hemoglobin level and drug dosage received in anemic cancer patients receiving darbepoetin alfa (*n* = 55)

Variable	Baseline, M (SD)	Wk 1, M (SD)	Wk 2, M (SD)	Wk 3, M (SD)	Wk 4, M (SD)	Wk 7, M (SD)	Wk 10, M (SD)	Wk 13, M (SD)	<i>p</i> -value for interaction
Hemoglobin, g/l									
DAL (<i>n</i> = 29)	101.2 (8.1)	102.9 (9.7)	108.0 (12.3)	110.2 (11.6)	111.3 (11.4)	116.2 (13.0)	117.4 (11.1)	123.4 (12.8)	.085, .067 ^a
DEX (<i>n</i> = 26)	103.9 (6.4)	106.1 (9.4)	108.5 (12.2)	113.9 (10.5)	119.6 (13.3)	122.5 (13.8)	118.4 (13.8)	120.6 (16.3)	
Drug dosage, μg/kg									
DAL (<i>n</i> = 29)	4.49 (.05)	4.31 (.84)	4.33 (.84)	4.34 (0.84)	4.25 (0.92)	3.53 (1.84)	3.55 (1.74)	NA	.181, .124 ^a
DEX (<i>n</i> = 26)	4.51 (.04)	4.50 (.01)	4.33 (.88)	4.16 (1.22)	3.42 (1.92)	3.03 (2.11)	2.94 (2.09)	NA	

^aAdjusted for baseline value, age, sex, marital status, education, primary tumor type, metastatic disease, current chemotherapy, and prior blood transfusion.
Abbreviations: DAL, darbepoetin alone; DEX, darbepoetin plus exercise; M, mean; NA, not available; SD, standard deviation.

Associations Between Exercise Adherence and Changes in Endpoints

Pearson correlations indicated that higher exercise adherence was associated with greater improvements in VO_{2peak} and peak watts (online supplementary Table 1). Moreover, a greater Hb response was associated with greater improvements in VO_{2peak}, peak watts, fatigue, and QoL. Finally, improvements in VO_{2peak} and peak watts were associated with improvements in fatigue and QoL. In multiple regression analyses, Hb change ($\beta = 0.33$; *p* = .018) but not

VO_{2peak} change ($\beta = 0.17$; *p* = .221) was independently associated with QoL improvements. Similar findings were observed for fatigue (Hb change: $\beta = 0.30$; *p* = .030; VO_{2peak} change: $\beta = 0.19$; *p* = .155).

DISCUSSION

The EXTRA trial evaluated the effects of darbepoetin alfa plus aerobic exercise training compared with darbepoetin alfa alone on patient-rated and objective outcomes. Our trial demonstrated that a moderate-to-vigorous aerobic ex-

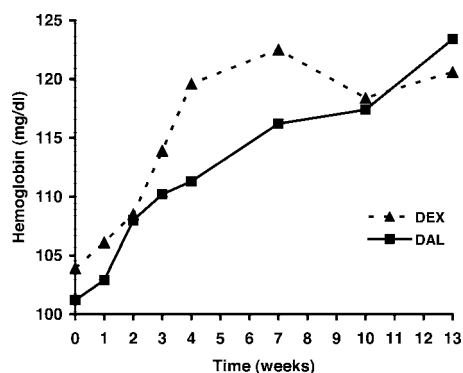


Figure 2. Hemoglobin levels across the intervention by group assignment.

Abbreviations: DAL, darbepoetin alfa alone; DEX, darbepoetin alfa plus exercise training.

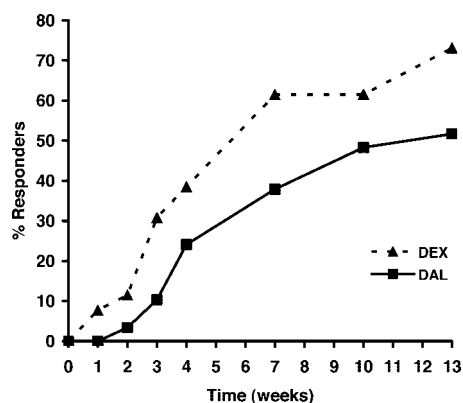


Figure 3. Percentage of participants achieving a hemoglobin response of ≥ 20 g/l across the intervention by group assignment.

Abbreviations: DAL, darbepoetin alfa alone; DEX, darbepoetin alfa plus exercise training.

exercise intervention can be delivered safely in this setting with excellent adherence. Although our trial indicated that aerobic exercise training did not further improve QoL or fatigue, it did demonstrate substantial improvements in exercise capacity and trends toward a more rapid Hb response with less drug administration.

The failure of exercise training to improve QoL and fatigue over DAL in our trial may be a result of a lack of power from a small sample size and/or the large improvements in these outcomes with darbepoetin alfa alone. The improvements in the DAL group of 20 points on the FACT-An and 9 points on the fatigue subscale are about three times the minimally important differences on these scales [18] and are larger than those reported in recent systematic reviews and meta-analyses of ESAs [22, 23]. Given the absence of a non-ESA group, it is possible that such improvements were the result of greater attention and/or the passage of time. Nevertheless, our multiple regression analyses demonstrated that Hb improvement, and not improve-

ment in the VO_{2peak} , predicted QoL and fatigue. These data suggest that improving Hb, rather than VO_{2peak} , may be the more important mechanism for improving QoL and fatigue in anemic cancer patients. Finally, the global measure of QoL that we used may be too broad to detect the likely narrower effects of exercise training on the physical functioning component of QoL [24].

Consistent with our hypotheses, aerobic exercise training improved cardiovascular fitness over darbepoetin alfa alone. Specifically, darbepoetin alfa alone resulted in a non-significant increase in VO_{2peak} of 0.6 ml/kg per minute (3.7%), compared with an increase of 3.5 ml/kg per minute (22.4%) with the addition of exercise training. Although it is not currently known if a 3.5 ml/kg per minute improvement (equivalent to 1 metabolic equivalent) in VO_{2peak} is clinically meaningful among cancer patients, Gulati et al. [25] reported that a 1 metabolic equivalent difference in exercise capacity corresponded to a 17% difference in survival among 6,000 women without a history of breast cancer. Future studies are required to examine the prognostic value of exercise capacity among cancer patients with both early and advanced cancer.

While some studies have shown that ESA administration can improve exercise capacity in cancer patients and other clinical populations [26–29], the resulting improvements are often small and not as great as would be expected with the observed increases in oxygen-carrying capacity. In combination with our results, these studies suggest that, while ESAs increase the oxygen-carrying capacity of blood (via an increase in Hb), combining this treatment with exercise training provides a greater benefit to overall exercise capacity. The mechanisms of improvement from exercise training likely include improved oxygen delivery via increased blood volume, cardiac output, and tissue oxygen extraction by the working muscles [30].

Our study suggested a synergistic effect between ESAs and aerobic exercise on Hb response, as evidenced by a more rapid achievement of Hb response and a higher rate of Hb response. This effect was achieved with fewer ESA injections and a lower drug dose, further supporting the notion of an interaction between ESA therapy and aerobic exercise training. At present, the mechanisms for this interaction are not clear, although potential explanations include the effects of exercise training on growth hormone [31, 32], insulin-like growth factor [33, 34], tissue oxygenation [35], arterial hypoxemia, blood volume expansion [36], and reduced inflammation [37]. These explanations are speculative, however, and further research is required to replicate this finding and determine the underlying mechanism(s) of this response.

While achieving a faster Hb response would intuitively

seem to be a desirable outcome in patients with anemia (quicker attenuation of patient symptoms, lower medication requirement, and lower cost), these potential benefits may be offset by recent data suggesting that, because of the association with venous thromboembolism, gradual increases in Hb may be preferred [2]. Similarly, while a substantial rate of Hb response (73%) was observed in the DEX group, recent clinical studies have suggested higher risks for certain adverse events when patients were treated to target Hb levels >120 g/l [6, 38, 39]. Furthermore, the administration of ESAs is now contraindicated in all patients not receiving chemotherapy, because recent studies have shown a negative effect on overall survival in head and neck cancer patients [40], non-small cell lung cancer patients not receiving chemotherapy [7], and cancer patients with active malignant disease not receiving chemotherapy and/or radiation therapy [39]. It is unclear, however, if the adverse effect of ESAs is a result of the higher Hb level itself or if it is a direct effect of the drug on the tumor [41]. If the Hb itself is the cause, then our trial showing that exercise training produces a more rapid Hb response is cause for concern. If the direct effect of the drug is the cause, then our result is potentially attractive because it shows that exercise can produce a more rapid Hb response with less drug.

The strengths and limitations of this study deserve mention. Strengths include being one of the first trials to examine the effects of supervised exercise training during ESA treatment in anemic cancer patients, the randomized controlled trial design, the well-defined population, the excellent adherence rate, and the minimal loss to follow-up. Limitations include the lack of an exercise-only study arm, the failure to achieve our recruitment goal, the 24% recruitment rate that restricts generalizability, the short intervention, and the lack of mechanistic data. Additionally, 7% of the study participants were not receiving concurrent chemotherapy at the time of initiation of ESA therapy. Such use is now thought to be unsafe outside a clinical trial, given recent safety concerns raised in this population [5, 7, 41].

In summary, our trial demonstrates that exercise train-

ing during ESA administration is safe and feasible, and leads to meaningful improvements in cardiorespiratory fitness. Exercise training may also potentiate the effects of ESAs on Hb response, but this finding requires confirmation in larger studies. While there are increasing concerns about producing a rapid rise in Hb, “overshooting” a target Hb of 120 g/l, and use in patients not receiving chemotherapy is now contraindicated, our study identified no safety signals that would preclude aerobic exercise training in anemic patients initiating guideline-based ESA therapy.

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 Kerry S. Courneya and John R. Mackey had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Effects of Aerobic Exercise Training in Anemic Cancer Patients Receiving
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