VOLUME 27 · NUMBER 27 · SEPTEMBER 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Randomized Controlled Trial of the Effects of Aerobic Exercise on Physical Functioning and Quality of Life in Lymphoma Patients

Kerry S. Courneya, Christopher M. Sellar, Clare Stevinson, Margaret L. McNeely, Carolyn J. Peddle, Christine M. Friedenreich, Keith Tankel, Sanraj Basi, Neil Chua, Alex Mazurek, and Tony Reiman

From the University of Alberta; Cross Cancer Institute, Edmonton; Alberta Cancer Board, Calgary, Alberta, Canada; and University of Manchester, Manchester, United Kingdom.

Submitted September 9, 2008; accepted May 14, 2009; published online ahead of print at www.jco.org on August 17, 2009.

Supported by the Lance Armstrong Foundation. Additional support provided by the Canada Research Chairs Program (K.S.C.); by Health Studentships (C.M.S. and C.J.P.), Senior Health Scholar Award (C.M.F.), and Clinical Investigator Award (T.R.) from the Alberta Heritage Foundation for Medical Research; by Research Team Grant No. 010282 from the National Cancer Institute of Canada (NCIC); and by the Canadian Cancer Society (CCS) and the NCIC/CCS Sociobehavioral Cancer Research Network (K.S.C. and C.M.F.).

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Kerry S. Courneya, PhD, Faculty of Physical Education and Recreation, University of Alberta, E-488 Van Vliet Center, Edmonton, AB, Canada T6G 2H9; e-mail: kerry.courneya@ualberta.ca.

The Acknowledgment is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

0732-183X/09/2727-4605/$20.00

DOI: 10.1200/JCO.2008.20.0634

ABSTRACT

Purpose
Lymphoma patients commonly experience declines in physical functioning and quality of life (QoL) that may be reversed with exercise training.

Patients and Methods
We conducted a randomized controlled trial in Edmonton, Alberta, Canada, between 2005 and 2008 that stratified 122 lymphoma patients by major disease type and current treatment status and randomly assigned them to usual care (UC; n = 62) or 12 weeks of supervised aerobic exercise training (AET; n = 60). Our primary end point was patient-rated physical functioning assessed by the Trial Outcome Index-Anemia. Secondary end points were overall QoL, psychosocial functioning, cardiovascular fitness, and body composition.

Results
Follow-up assessment for our primary end point was 96% (117 of 122) at postintervention and 90% (110 of 122) at 6-month follow-up. Median adherence to the supervised exercise program was 92%. At postintervention, AET was superior to UC for patient-rated physical functioning (mean group difference, +9.0; 95% CI, 2.0 to 16.0; $P = .012$), overall QoL ($P = .021$), fatigue ($P = .013$), happiness ($P = .004$), depression ($P = .005$), general health ($P < .001$), cardiovascular fitness ($P < .001$), and lean body mass ($P = .008$). Change in peak cardiovascular fitness mediated the change in patient-rated physical functioning. AET did not interfere with chemotherapy completion rate or treatment response. At 6-month follow-up, AET was still borderline or significantly superior to UC for overall QoL ($P = .054$), happiness ($P = .034$), and depression ($P = .009$) without an increased risk of disease recurrence/progression.

Conclusion
AET significantly improved important patient-rated outcomes and objective physical functioning in lymphoma patients without interfering with medical treatments or response. Exercise training to improve cardiovascular fitness should be considered in the management of lymphoma patients.

J Clin Oncol 27:4605-4612. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Lymphoma is the fifth most common cancer in the United States and Canada with 75,000 Americans and 8,000 Canadians diagnosed in 2008.[1,2] Non-Hodgkin's lymphoma (NHL) comprises 89% of lymphomas with the remainder being Hodgkin's lymphoma (HL). Five-year relative survival is 63% for NHL and 85% for HL. Lymphoma patients are often treated multiple times with chemotherapy, radiation therapy, and/or biologic therapy interspersed with active surveillance. The disease and its repeated treatments can produce adverse effects including physical deconditioning, body composition changes, fatigue, depression, and reduced quality of life (QoL).[3-6] Few interventions have been shown to improve these outcomes.

Exercise training improves health outcomes in breast[7] and prostate[8] cancer patients but no randomized controlled trials (RCTs) have focused on lymphoma patients.[9] Generalizing from breast and prostate to lymphoma may be unwise given differences in demographics, disease pathology, prognosis, treatments, and symptoms/adverse effects. Here, we report results from the Healthy Exercise for Lymphoma Patients (HELP) trial which, to the best of our knowledge, is the first exercise RCT in lymphoma patients. We hypothesized that aerobic exercise training (AET) would be superior to usual care (UC) for patient-rated outcomes (PROs),

cardiovascular fitness, and body composition. We also expected cardiovascular fitness improvements to mediate improvements in the PROs. We included patients receiving chemotherapy or off treatments to explore potential differences in response. Chemotherapy completion rate, treatment response, and disease recurrence were monitored for safety purposes and considered exploratory end points.

PATIENTS AND METHODS

The study was a single-center, two-armed RCT. Ethical approval was obtained from the Alberta Cancer Board and the University of Alberta, and written informed consent was obtained from participants.

Setting and Participants

Participants were recruited from the Cross Cancer Institute in Edmonton, AB, Canada. Eligibility criteria included English speaking, ≥ 18 years old, histologically confirmed HL or NHL, and receiving chemotherapy or no treatments. Patients receiving chemotherapy may have started treatment before enrollment but needed to have at least 8 weeks of planned treatment remaining. Patients not receiving treatments had to have no planned treatments during the intervention period. Patients were excluded if they had uncontrolled hypertension, cardiac illness, lived more than 80 km from the facility, or otherwise were not approved by their oncologist. Patients were not excluded on the basis of baseline exercise in order to mimic clinical practice. If randomly assigned to AET, participants were asked to complete the program in addition to their baseline exercise. Eligible patients were identified by seven treating oncologists and a mailed invitation using the Alberta Cancer Registry on the basis of the same eligibility criteria. Patients recruited through the mail obtained approval from their treating oncologist. Our goal was to recruit approximately 50% of patients receiving chemotherapy and 50% off treatment.

Randomization and Blinding

After completing baseline tests, participants were stratified by major disease type (HL, indolent NHL, aggressive NHL) and current treatment status (chemotherapy, off treatments) and were randomly assigned to AET or UC by using a computer-generated program. The allocation sequence was generated independently and concealed in opaque envelopes from the study coordinator who assigned participants to groups. Outcomes assessors were not always blinded to group assignment but were trained in standardizing testing procedures.

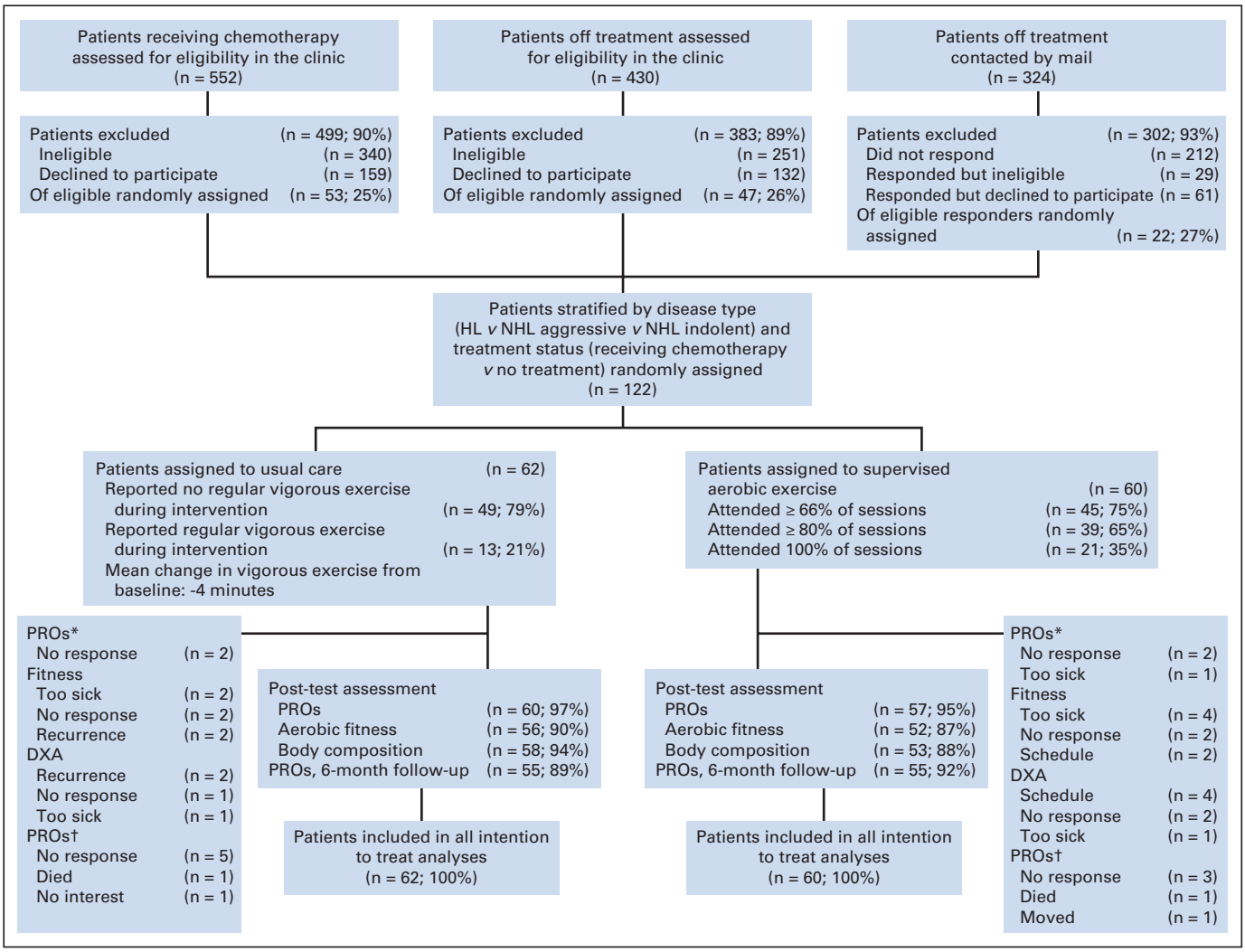

Fig 1. CONSORT diagram showing flow of participants through the trial. (*) Postintervention; (†) 6-month follow-up. HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; PRO, patient-rated outcome; DXA, dual energy x-ray absorptiometry.

Intervention

Participants randomly assigned to AET received an exercise program designed to maximize cardiovascular fitness on the basis of research suggesting that cardiovascular fitness improvements may optimize PROs.[10] Sessions were supervised by exercise physiologists and completed on an upright or recumbent cycle ergometer (Life Fitness, Schiller Park, IL) three times per week for 12 weeks. Intensity began at 60% of the peak power output, which corresponded with baseline peak oxygen consumption (VO_{2peak}), and was increased by 5% each week to 75% by the fourth week. Duration began at 15 to 20 minutes for the first 4 weeks and increased by 5 minutes per week to 40 to 45 minutes in the ninth week. On the basis of research suggesting that interval training can maximize cardiovascular fitness improvements in cancer patients,[11] we instituted one session per week of interval training above the ventilatory threshold in week 7 and one session of VO_{2peak} interval training in week 9. To maximize adherence, we incorporated behavioral support techniques based on the theory of planned behavior,[12] including an attractive facility, flexible hours, scheduled exercise sessions, telephone follow-up after missed sessions, positive reinforcement from staff, variation in exercise, and paid parking. UC participants were asked not to increase exercise above baseline and were offered 4 weeks supervised exercise after postintervention assessments.

Assessment of Primary and Secondary End Points

PROs were assessed at baseline (before random assignment), postintervention, and at 6-month follow-up. The primary time point of interest was postintervention, and the primary end point was patient-rated physical functioning assessed by the Trial Outcome Index-Anemia (TOI-An) from the well-validated Functional Assessment of Cancer Therapy-Anemia (FACT-An) scale.[13] We selected the TOI-An as the primary end point because exercise may be particularly beneficial for the physical functioning aspects of QoL.[7] We also analyzed the total FACT-An and the Fatigue subscale. Happiness was assessed by the Happiness scale[14]; depression by the short-form (SF) Center for Epidemiological Studies-Depression scale[15]; anxiety by the SF Spielberger State Anxiety Inventory[16]; lymphoma symptoms by the lymphoma subscale from the FACT[17]; and general health by the single item from the SF12[18] asking respondents to rate their health from poor to excellent.

Objective fitness outcomes were assessed at baseline and postintervention. Cardiovascular fitness was assessed by a maximal graded exercise test administered by an exercise physiologist with physician-supervised ECG monitoring (CardioStress ECG; Nassif Associates, Central Square, NY). The protocol for this test has been published,[19] and it follows American Thoracic Society guidelines.[20] Metabolic data were averaged over 15 seconds, with the highest 15-second VO_2 value recorded as VO_{2peak} and the corresponding power output recorded as peak power output. Ventilatory threshold was determined by using the ventilatory equivalent method.[20]

Body weight and standing height were assessed using a balance beam scale (Health o meter, Shelton, CT). Dual x-ray absorptiometry assessed body composition (General Electric Healthcare, Piscataway, NJ). For participants receiving chemotherapy, treatment completion rate was assessed as the number of cycles completed divided by the minimal and maximal number of cycles planned. Treatment response was recorded as progressive, stable, partial response, or complete response (unconfirmed and confirmed). For all participants, progression or recurrence at 6-month follow-up was abstracted from medical records.

Assessment of Covariates, Adherence, and Adverse Events

Demographic and behavioral data were collected by self-report. Medical data were abstracted from medical records. Exercise trainers monitored adherence and adverse events. Nonprotocol exercise was assessed using self-report.[21]

Data Analyses

Sixty participants per group provided a 0.80 power to detect a change score difference of 10 (standard deviation = 18) on the TOI-An with 10% loss to follow-up and two-tailed alpha less than .05. Linear mixed-model analysis modeled each outcome measure at two time points (either baseline and postintervention or baseline and 6-month follow-up) and compared the differences between groups in changes over time using intention-to-treat analyses and all available data.[22] Our primary analysis was unadjusted, but we also conducted analyses adjusted for baseline value of the outcome, disease type, stage, treatment status, age, sex, and baseline exercise (defined as $\geq$ 150 minutes of moderate exercise per week). We also used mixed-model analysis to assess effect modification by our stratification variables (major disease type and treatment status) in an interaction test.[22] Patient-rated general health was categorized as worsened (declined at least one category), stable (no change in category), or improved (increased at least one category) and analyzed using χ^2 analysis for participants with complete data. Chemotherapy completion rate, initial treatment response, and recurrence/progression during follow-up were also analyzed using χ^2 analysis and included all participants because no treatment data were missing. Multiple regression was used to test the mediating role of cardiovascular fitness for postintervention PRO change scores in participants with complete data.[23] This approach requires that the outcome of interest (the PRO) be regressed on the proposed mediator (fitness) and the intervention (group assignment coded as 0 = UC and 1 = AET). Mediation is present when the proposed mediator maintains a significant relationship with the outcome whereas group assignment does not.

RESULTS

Recruitment occurred between May 2005 and May 2008. We recruited 9% (122 of 1,306) of screened patients and 26% (122 of 474) of eligible patients (Fig 1). Reasons for ineligibility were living more than 80 km from the facility (n = 268), treatment adverse effects (n = 90), serious conditions (n = 86), and frailty (n = 82). Reasons for refusal were too busy (n = 83), no reason (n = 70), not interested (n = 40), transportation issues (n = 40), and currently exercising (n = 30). We obtained postintervention data on the PROs from 117 of 122 (96%) participants and 6-month data from 110 of 122 (90%) participants. Groups were balanced on baseline covariates (Table 1). The AET group attended a mean of 77.8% (28.0 of 36) and a median of 91.7% (33.0 of 36) of the supervised sessions. Duration and intensity were met during 99.0% (27.8 of 28.0) and 90.7% (25.4 of 28.0) of the supervised sessions, respectively. Fewer than 25% reported regular exercise outside of the trial in either group ($P = .71$). Twenty-six of 62 (42%) UC participants attended supervised exercise after postintervention assessments.

Changes in PROs at Postintervention

At postintervention, AET was superior to UC for patient-rated physical functioning ($P = .012$), overall QoL ($P = .021$), fatigue ($P = .013$), happiness ($P = .004$), and depression ($P = .005$; Table 2). Results remained significant after adjustment (Table 2). General health was improved in AET compared with UC ($P < .001$; Fig 2). Neither disease type (P for interaction = 0.46; Fig 3A) nor current treatment status (P for interaction = 0.70; Fig 4A) moderated the effects of AET on the TOI-An (or any other PROs; data not presented).

Changes in Objective Fitness Outcomes at Postintervention

At postintervention, AET was superior to UC on all indicators of cardiovascular fitness (P values $< .001$) and lean body mass ($P = .008$) and for percent body fat after adjustments ($P = .050$; Table 3). Neither disease type (P for interaction = 0.21; Fig 3B) nor current treatment

Table 1. Baseline Characteristics of Participants, Overall and by Group Assignment

Characteristic	Overall (N = 122)		Usual Care (n = 62)		Aerobic Exercise Training (n = 60)		*P*
	No.	%	No.	%	No.	%	
Demographic profile							
Age, years							.809
Mean	53.2		53.5		52.8		
Range	18-80		18-80		18-77		
18-39	22	18.0	12	19.4	10	16.7	
40-59	51	41.8	25	40.3	26	43.3	
≥ 60	49	40.2	25	40.3	24	40.0	
Male	72	59.0	35	56.5	37	61.7	.558
Married	94	77.0	46	74.2	48	80.0	.446
Completed university	63	51.6	32	51.6	31	51.7	.995
Income > $60,000/year*	73	62.9	39	62.9	34	63.0	.995
Employed	54	44.3	32	51.6	22	36.7	.097
Cancer profile							
Major cancer type							.978
NHL indolent	52	42.6	27	43.5	25	41.7	
NHL aggressive	48	39.3	24	38.7	24	40.0	
Hodgkin's lymphoma	22	18.0	11	17.7	11	18.3	
Most common cancer subtypes							.472
Diffuse large B cell	42	34.4	21	33.9	21	35.0	
Follicular	29	23.8	15	24.2	14	23.3	
Nodular sclerosing	19	15.6	10	16.1	9	15.0	
Chronic lymphocytic leukemia	14	11.5	10	16.1	4	6.7	
Disease stage							.653
I	18	14.8	7	11.3	11	18.3	
II	23	18.9	15	24.2	8	13.3	
III	17	13.9	8	12.9	9	15.0	
IV	28	23.0	13	21.0	15	25.0	
No evidence of disease	34	27.9	18	29.0	16	26.7	
Unclear	2	1.6	1	1.6	1	1.7	
Previous treatments							
Chemotherapy	54	44.3	28	45.2	26	43.3	.839
Radiation therapy	28	23.0	15	24.2	13	21.7	.740
Current treatment status							.599
Chemotherapy	54	44.3	26	41.9	28	46.7	
Off treatment	68	55.7	36	58.1	32	53.3	
Time since diagnosis, months							.234
Mean	29.2		33.0		25.3		
SD	35.6		39.0		31.5		
Health profile							
Most common comorbidities							
Arthritis	38	31.1	14	22.6	24	40.0	.038
Hypercholestremia	36	29.5	18	29.0	18	30.0	.907
Hypertension	35	28.7	21	33.9	14	23.3	.198
Weight, kg							.243
Mean	80.1		78.5		81.8		
SD	16.0		17.1		14.8		
BMI, kg/m^2							.470
Mean	27.1		26.7		27.4		
SD	4.9		5.4		4.5		
Healthy weight	42	34.4	25	40.3	17	28.3	
Overweight	47	38.5	20	32.3	27	45.0	
Obese	33	27.0	17	27.4	16	26.7	
Current smoker	13	10.7	9	14.5	4	6.7	.160
Baseline exerciser	35	28.7	23	37.1	12	20.0	.037

Abbreviations: NHL, non-Hodgkin's lymphoma; SD, standard deviation; BMI, body mass index.
*n = 116.

Table 2. Effects of Aerobic Exercise Training on Patient-Rated Outcomes at Postintervention in Lymphoma Patients

Outcome	Baseline		Post-Test		Mean Change		Unadjusted Group Difference in Mean Change			Adjusted Group Difference in Mean Change		
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*P*	Mean	95% CI	*P*
TOI-An, 0-136												
UC	105.1	21.1	105.4	22.0	+0.4	−4.5 to 5.3	+9.0	2.0 to 16.0	.012	+7.2	1.3 to 13.1	.017
AET	100.1	21.9	109.3	18.7	+9.4	4.4 to 14.4						
FACT-An, 0-188												
UC	147.1	24.3	148.1	25.7	+ 1.1	−4.5 to 6.7	+9.5	1.5 to 17.5	.021	+7.2	0.4 to 14.1	.039
AET	140.7	26.8	151.4	21.7	+10.6	4.9 to 16.3						
Fatigue, 0-52												
UC	38.0	10.7	38.0	11.1	−0.1	−2.7 to 2.4	+4.6	1.0 to 8.3	.013	+4.0	0.9 to 7.0	.012
AET	36.1	10.8	40.5	9.4	+4.5	1.9 to 7.1						
Happiness, 0-100												
UC	66.9	19.2	67.2	18.5	+ 0.7	−4.0 to 5.5	+10.0	3.2 to 16.7	.004	+6.8	1.4 to 12.3	.015
AET	59.6	22.4	70.9	16.4	+10.7	5.9 to 15.5						
Depression, 0-30												
UC	6.0	4.5	6.1	5.0	+0.2	−1.0 to 1.3	−2.4	−4.0 to −0.7	.005	−1.6	−3.0 to −0.1	.031
AET	7.7	5.7	5.4	4.5	−2.2	−3.4 to −1.0						
Anxiety, 10-40												
UC	16.9	5.4	16.2	5.2	−0.6	−2.0 to 0.8	−1.0	−3.0 to 1.0	.323	−0.4	−2.1 to 1.3	.642
AET	18.4	6.6	16.5	5.2	−1.6	−3.0 to −0.2						
Lymphoma symptoms, 0-60												
UC	47.7	8.7	49.3	8.2	+1.5	−0.1 to 3.1	+1.2	−1.1 to 3.5	.306	+1.3	−0.7 to 3.2	.199
AET	47.4	8.7	50.3	7.2	+2.7	1.1 to 4.4						

NOTE. Mean and SD at post-test are based on available data. Mean change is estimated on the basis of mixed model analysis. Adjusted group difference in mean change was adjusted for baseline value of the outcome, major cancer type, disease stage, current treatment status, age, sex, and baseline exercise. Possible range of scale shown next to patient-rated outcomes in left column.

Abbreviations: SD, standard deviation; TOI-An, Trial Outcome Index-Anemia; UC, usual care; AET, aerobic exercise training; FACT-An, Functional Assessment of Cancer Therapy-Anemia.

status (*P* for interaction = 0.40; Fig 4B) moderated the effects of AET on VO_{2peak} (or any other fitness outcome; data not presented).

Chemotherapy Completion Rate and Treatment Response

For participants receiving chemotherapy (n = 54), the AET group (n = 28) completed 103% of its planned minimum and 94% of its planned maximum cycles compared with 99% (*P* = .45) and 89% (*P* = .20) for UC (n = 26), respectively. A complete response (confirmed or unconfirmed) was achieved by 46.4% (13 of 28) in the AET group and 30.8% (8 of 26) in the UC group (*P* = .24).

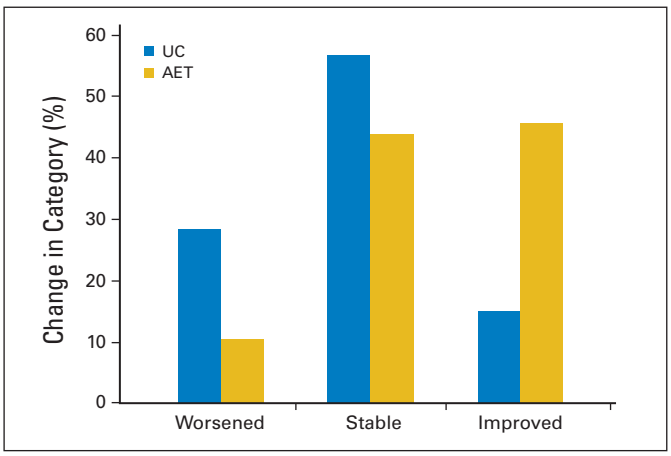

Fig 2. Category change in patient-rated general health by group assignment. UC, usual care; AET, aerobic exercise training.

Mediation of PROs by Objective Fitness Outcomes

Change in VO_{2peak} mediated the effect of the intervention on change in the TOI-An (VO_{2peak}: $\beta = .29$; $P = .026$; group assignment: $\beta = .02$; $P = .90$). Borderline significant mediation was observed for fatigue (VO_{2peak}: $\beta = .23$; $P = .073$; group assignment: $\beta = .05$; $P = .71$) and the FACT-An (VO_{2peak}: $\beta = .21$; $P = .10$; group assignment: $\beta = .05$; $P = .69$). VO_{2peak} did not mediate the effects of AET on happiness (VO_{2peak}: $\beta = .03$; $P = .83$; group assignment: $\beta = .28$; $P = .032$) or depression (VO_{2peak}: $\beta = -.14$; $P = .29$; group assignment: $\beta = -.17$; $P = .19$). Other objective fitness indicators did not mediate (data not presented).

Six-Month Follow-Up

At 6-month follow-up, changes in patient-rated physical functioning favored the AET group but did not reach statistical significance (mean difference, +5.5; 95% CI, −1.5 to 12.4; *P* = .121). There was a borderline significant change in favor of AET for overall QoL (mean difference, +7.6; 95% CI, −0.1 to 15.4; *P* = .054), and a significant difference for happiness (mean difference, +8.9; 95% CI, 0.7 to 17.1; *P* = .034) and depression (mean difference, −2.5; 95% CI, −0.6 to −4.4; *P* = .009). Recurrence/progression during the 6-month follow-up was noted in 6.7% (4 of 60) of the AET group and 11.3% (7 of 62) of the UC group (*P* = .37). Regular exercise was reported by 63.6% (35 of 55) in the AET group and 40.0% (22 of 55) in the UC group (*P* = .017).

Adverse Events

No serious events but three adverse events (back, hip, and knee pain) were related to exercise. The participant with knee pain withdrew from exercise whereas the two other participants continued with a modified exercise program.

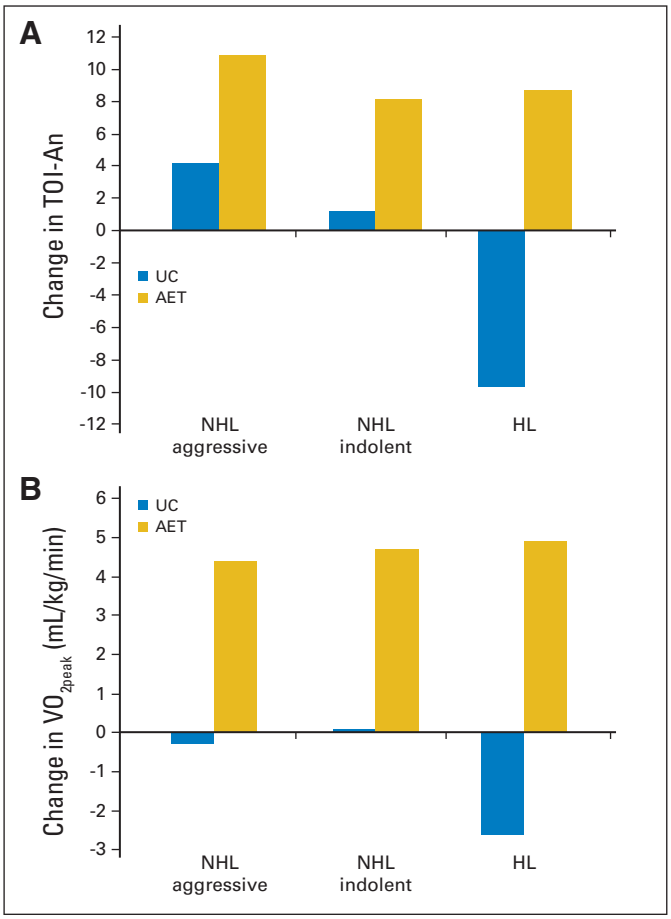

Fig 3. Change in (A) patient-rated physical functioning and (B) peak oxygen consumption (VO_{2peak}) by major disease type. TOI-An, Trial Outcome Index-Anemia; UC, usual care; AET, aerobic exercise training; NHL, non-Hodgkin's lymphoma; HL, Hodgkin's lymphoma.

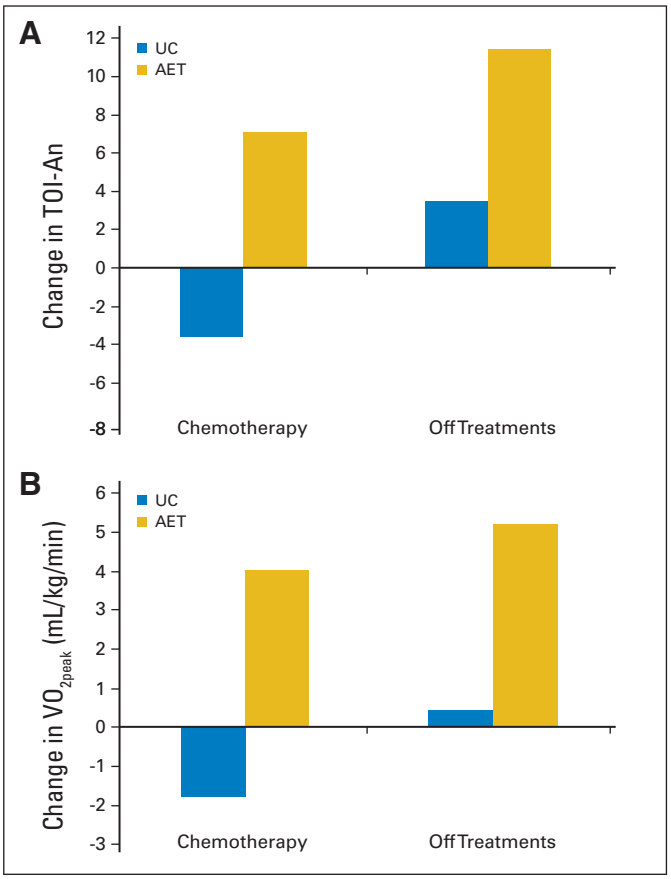

Fig 4. Change in (A) patient-rated physical functioning and (B) peak oxygen consumption (VO_{2peak}) by current treatment status. TOI-An, Trial Outcome Index-Anemia; UC, usual care; AET, aerobic exercise training.

DISCUSSION

Consistent with our hypotheses, AET significantly improved patient-rated physical functioning, overall QoL, fatigue, general health, happiness, depression, cardiovascular fitness, and lean body mass in lymphoma patients receiving chemotherapy or off treatments. Change in VO_{2peak} mediated the effect of the intervention on patient-rated physical functioning but not psychosocial functioning. Major disease type and current treatment status did not alter the results. For participants receiving chemotherapy, AET did not interfere with treatment completion or response. Some beneficial effects were still present at the 6-month follow-up despite substantial exercise crossover during follow-up.

The effects of AET on the PROs appear meaningful. The effect of 9.0 points on the TOI-An exceeds the 6.0 minimal important difference for this scale.[13] The effects on the FACT-An and fatigue scales of 9.6 and 4.6 also exceed the minimal important differences for these scales of 7.0 and 3.0, respectively.[13] Few published exercise studies in lymphoma patients are available for comparison.[9] A recent systematic review of 10 intervention studies in adult hematologic cancer patients treated with stem cell transplantation concluded that methodologic quality is poor to modest, and effectiveness has not been demonstrated. In a single-arm trial of nine HL patients with severe fatigue, Oldervoll et al[24] reported improvements in fatigue, physical functioning, and cardiovascular fitness after 20 weeks of unsupervised aerobic exercise. In a cross-sectional survey of 438 NHL survivors, Vallance et al[25] reported favorable associations between regular exercise and physical functioning, fatigue, and overall QoL.

Exercise RCTs in other cancer patient populations are available for comparison. In a meta-analysis of 14 RCTs involving 717 breast cancer patients, McNeely et al[7] reported a benefit of 6.6 points on the FACT-Breast scale and a standardized effect size (d) of 0.46 on fatigue. In a meta-analysis of 20 RCTs involving 1,662 mixed cancer patients, Cramp and Daniel[26] reported a small but significant overall effect of exercise on fatigue ($d = 0.23$) that was slightly larger for breast cancer patients ($d = 0.34$). Our improvement in fatigue is noteworthy, given the difficulty of managing this symptom in cancer patients.[27]

Our exercise intervention also improved cardiovascular fitness by more than 20%. This improvement is larger than that typically reported in other cancer patient populations[7,26] and may have resulted from our higher intensity training program supplemented with interval training. Improving cardiovascular fitness in lymphoma patients may have implications for disease outcomes and survival based on research in other populations,[28,29] although such associations have not been established in lymphoma patients or any other cancer patient populations. Improvements in lean body mass may also have implications for improved physical functioning, disease risk, and survival.[30]

Improvement in VO_{2peak} mediated the effects of AET on patient-rated physical functioning and was borderline significant for fatigue.

Table 3. Effects of Aerobic Exercise Training on Objective Fitness Outcomes at Postintervention in Lymphoma Patients

Outcomes	Baseline		Post-Test		Mean Change		Unadjusted Group Differences in Mean Change			Adjusted Group Differences in Mean Change		
	Mean	SD	Mean	SD	Mean	95% CI	Mean	95% CI	*P*	Mean	95% CI	*P*
VO_{2peak}, L/min												
UC	1.98	0.71	1.96	0.69	−0.03	−0.09 to 0.03	+0.43	0.34 to 0.52	< .001	+0.43	0.34 to 0.52	< .001
AET	2.02	0.66	2.38	0.81	+0.40	0.34 to 0.47						
VO_{2peak}, mL/kg/min												
UC	25.4	9.2	25.2	9.1	−0.6	−1.5 to 0.3	+5.2	4.0 to 6.5	< .001	+5.2	4.0 to 6.4	< .001
AET	24.7	7.2	29.4	8.6	+4.6	3.7 to 5.5						
Peak power output, watts												
UC	146	57	148	56	+2	−4 to 8	+29	20 to 37	< .001	+28	20 to 37	< .001
AET	148	56	176	69	+31	25 to 37						
Ventilatory threshold, L/min												
UC	1.09	0.37	1.04	0.35	−0.03	−0.09 to 0.02	+0.33	0.26 to 0.41	< .001	+0.33	0.26 to 0.41	< .001
AET	1.07	0.35	1.35	0.50	+0.32	0.16 to 0.48						
Body weight, kg												
UC	78.5	17.1	78.7	16.0	+0.5	−0.3 to 1.3	+0.6	−0.5 to 1.8	.276	+0.5	−0.6 to 1.6	.381
AET	81.8	14.8	81.5	16.0	+1.2	0.3 to 2.0						
Lean mass, kg												
UC	49.9	10.0	49.8	9.9	+0.1	−0.3 to 0.5	+0.8	0.2 to 1.4	.008	+0.8	0.2 to 1.4	.010
AET	52.4	10.9	52.3	11.5	+0.9	0.5 to 1.3						
Fat mass, kg												
UC	25.3	11.8	25.7	11.1	+0.6	−0.1 to 1.2	−0.3	−1.2 to 0.7	.589	−0.3	−1.3 to 0.5	.386
AET	25.8	9.5	26.0	10.1	+0.3	−0.4 to 1.0						
Body fat, %												
UC	32.6	10.9	33.2	10.5	+0.6	−0.1 to 1.2	−0.8	0.2 to −1.7	.110	−0.9	−0.0 to −1.7	.050
AET	32.6	9.9	32.8	10.1	−0.2	−0.8 to 0.5						

NOTE. Mean and SD at post-test are based on available data. Mean change is estimated on the basis of mixed model analysis. Adjusted group difference in mean change was adjusted for baseline value of the outcome, major cancer type, disease stage, current treatment status, age, sex, and baseline exercise.
Abbreviations: SD, standard deviation; VO_{2peak}, peak oxygen consumption; UC, usual care; AET, aerobic exercise training.

This finding is consistent with a previous trial in postadjuvant therapy breast cancer survivors[10] and with other trials that have reported associations between changes in objective fitness and PROs.[31,32] Interestingly, other fitness indicators did not mediate the effects of our intervention, suggesting that maximizing improvements in VO_{2peak} may be the best strategy for improving physical and functional aspects of QoL in lymphoma patients. Finally, consistent with our previous trial,[10] improvements in psychosocial outcomes (happiness and depression) were not mediated by fitness parameters, suggesting that other aspects of the intervention may explain these improved outcomes (eg, increased social interaction, distraction from cancer/treatments).

Our results were not modified by major disease type or current treatment status although we acknowledge that our trial was not powered to detect interactions. In terms of major disease type, it appears that the effects on the TOI-An and VO_{2peak} were larger for HL patients, but we had only 22 HL patients in the trial, and this difference could easily be due to chance. In terms of current treatment status, the magnitude of the effects on the TOI-An and VO_{2peak} were virtually identical, suggesting that even larger trials may not yield meaningful interaction effects based on treatment status. This finding is at odds with results from recent meta-analyses suggesting larger exercise effects in the postadjuvant setting compared with the adjuvant setting.[7,26] Importantly, these meta-analyses are based almost entirely on breast cancer trials and may not generalize to other cancer patient populations. Consistent with expectations, our trial showed that the benefits of exercise during chemotherapy consisted of both prevention of decline and actual gains in functioning whereas the off-treatment benefits consisted entirely of gains.

Importantly, our exercise training program did not interfere with lymphoma patients' ability or willingness to complete chemotherapy or their clinical response to treatment. We acknowledge that our trial was not powered to answer these questions; however, the differences favored the exercise group. Few exercise RCTs have tracked treatment factors. We recently reported that breast cancer patients engaged in resistance training completed a higher relative dose intensity of chemotherapy compared with UC,[31] but the finding was not expected and needs replication. At a minimum, it appears that vigorous intensity exercise during chemotherapy does not jeopardize treatment outcomes.

Our trial's strengths include being the first exercise RCT to focus on lymphoma patients, an adequate overall sample size, supervised exercise, excellent adherence, a comprehensive assessment of important outcomes with validated measures, intention-to-treat analysis, minimal loss to follow-up, and statistically and clinically meaningful effects on outcomes. Limitations include the heterogeneity of this patient population, our limited power to detect subgroup effects, the short 12-week exercise intervention, the 25% recruitment rate from a single center, the substantial exercise crossover during follow-up that likely attenuated group differences at 6 months, and the 15 postintervention group comparisons that would likely result in one false discovery if all comparisons were null. In terms of dissemination, this intervention could be implemented at other cancer centers and community-based fitness centers with appropriate facilities and

qualified staff. Given its sophistication in terms of exercise training principles, it is unclear if such a program could be self-directed by patients with minimal or no supervision.

In summary, our trial provides the first compelling evidence of the safety and effectiveness of exercise training in lymphoma patients. Our mediation analyses suggest that improvements in peak cardiovascular fitness may explain the improvements in physical and functional aspects of QoL. These data suggest a unique and important role for exercise in cancer care given that physical and functional aspects of QoL are often the most compromised in cancer patients and even long-term survivors.[33,34] Exercise training may be considered as a supportive care intervention for lymphoma patients receiving chemotherapy or off treatments. Additional research on the optimal type, volume, fractionation, and timing of exercise in this understudied patient population is warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Kerry S. Courneya, Christopher M. Sellar, Christine M. Friedenreich, Tony Reiman
Financial support: Kerry S. Courneya, Christine M. Friedenreich, Tony Reiman
Administrative support: Kerry S. Courneya, Clare Stevinson, Margaret L. McNeely, Carolyn J. Peddle, Alex Mazurek, Tony Reiman
Provision of study materials or patients: Kerry S. Courneya, Keith Tankel, Sanraj Basi, Neil Chua, Tony Reiman
Collection and assembly of data: Kerry S. Courneya, Christopher M. Sellar, Clare Stevinson, Margaret L. McNeely, Carolyn J. Peddle, Keith Tankel, Sanraj Basi, Neil Chua, Alex Mazurek, Tony Reiman
Data analysis and interpretation: Kerry S. Courneya, Christopher M. Sellar, Clare Stevinson, Margaret L. McNeely, Carolyn J. Peddle, Christine M. Friedenreich, Keith Tankel, Sanraj Basi, Neil Chua, Alex Mazurek, Tony Reiman
Manuscript writing: Kerry S. Courneya, Christopher M. Sellar
Final approval of manuscript: Kerry S. Courneya, Christopher M. Sellar, Clare Stevinson, Margaret L. McNeely, Carolyn J. Peddle, Christine M. Friedenreich, Keith Tankel, Sanraj Basi, Neil Chua, Alex Mazurek, Tony Reiman

REFERENCES

1. American Cancer Society: Cancer Facts & Figures 2008. Atlanta, GA, American Cancer Society, 2008
2. Canadian Cancer Society/National Cancer Institute of Canada: Canadian Cancer Statistics 2008. Toronto, ON, Canada, April 2008
3. Elbl L, Vasova I, Tomaskova I, et al: Cardiopulmonary exercise testing in the evaluation of functional capacity after treatment of lymphomas in adults. Leuk Lymphoma 47:843-851, 2006
4. Mols F, Aaronson NK, Vingerhoets AJ, et al: Quality of life among long-term non-Hodgkin lymphoma survivors: A population-based study. Cancer 109:1659-1667, 2007
5. Smith SK, Zimmerman S, Williams CS, et al: Post-traumatic stress outcomes in non-Hodgkin's lymphoma survivors. J Clin Oncol 26:934-941, 2008
6. Hjermstad MJ, Fossa SD, Oldervoll L, et al: Fatigue in long-term Hodgkin's disease survivors: A follow-up study. J Clin Oncol 23:6587-6595, 2005
7. McNeely ML, Campbell KL, Rowe BH, et al: Effects of exercise on breast cancer patients and survivors: A systematic review and meta-analysis. CMAJ 175:34-41, 2006
8. Thorsen L, Courneya KS, Stevinson C, et al: A systematic review of physical activity in prostate cancer survivors: Outcomes, prevalence, and determinants. Support Care Cancer 16:987-997, 2008
9. Liu RD, Chinapaw MJ, Huijgens PC, et al: Physical exercise interventions in haematological cancer patients, feasible to conduct but effectiveness to be established: A systematic literature review. Cancer Treat Rev 35:185-192, 2008
10. Courneya KS, Mackey JR, Bell GJ, et al: Randomized controlled trial of exercise training in postmenopausal breast cancer survivors: Cardiopulmonary and quality of life outcomes. J Clin Oncol 21:1660-1668, 2003
11. Courneya KS, Jones LW, Peddle CJ, et al: Effects of aerobic exercise training in anemic cancer patients receiving darbepoetin alfa: A randomized controlled trial. Oncologist 13:1012-1020, 2008
12. Ajzen I: The theory of planned behavior. Organ Behav Hum Decis Process 50:179-211, 1991
13. Cella D, Eton DT, Lai JS, et al: Combining anchor and distribution-based methods to derive minimal clinically important differences on the Functional Assessment of Cancer Therapy (FACT) anemia and fatigue scales. J Pain Symptom Manage 24:547-561, 2002
14. Fordyce MW: A review of research on the happiness measure: A sixty second index of happiness and mental health. Soc Indic Res 20:355-381, 1988
15. Kohout FJ, Berkman LF, Evans DA, et al: Two shorter forms of the CES-D (Center for Epidemiological Studies Depression) depression symptoms index. J Aging Health 5:179-193, 1993
16. Smith TW, Ingram RE, Brehm SS: Social anxiety, anxious self-preoccupation, and recall of self-relevant information. J Pers Soc Psychol 44:1276-1283, 1983
17. Cella D, Webster K, Cashy J, et al: Development of a measure of health-related quality of life for non-Hodgkin's lymphoma clinical research: The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym). Blood 106:750, 2005
18. Ware J Jr, Kosinski M, Keller SD: A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity. Med Care 34:220-233, 1996
19. Jones LW, Eves ND, Peddle CJ, et al: Effects of presurgical exercise training on cardiorespiratory fitness in patients undergoing thoracic surgery for malignant lung lesions. Cancer 110:590-598, 2007
20. American Thoracic Society/American College of Chest Physicians: ATS/ACCP statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 167:211-277, 2003
21. Godin G, Shephard RJ: A simple method to assess exercise behavior in the community. Can J Appl Sport Sci 10:141-146, 1985
22. Diggle P, Heagerty P, Liang K, et al: Analysis of Longitudinal Data (ed 2). New York, NY, Oxford University Press, 2002
23. Baron RM, Kenny DA: The moderator-mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol 51:1173-1182, 1986
24. Oldervoll LM, Kaasa S, Knobel H, et al: Exercise reduces fatigue in chronic fatigued Hodgkins disease survivors: Results from a pilot study. Eur J Cancer 39:57-63, 2003
25. Vallance JK, Courneya KS, Jones LW, et al: Differences in quality of life between non-Hodgkin's lymphoma survivors meeting and not meeting public health exercise guidelines. Psychooncology 14:979-991, 2005
26. Cramp F, Daniel J: Exercise for the management of cancer-related fatigue in adults. Cochrane Database Syst Rev 2: CD006145, 2008
27. Jacobsen PB, Donovan KA, Vadaparampil ST, et al: Systematic review and meta-analysis of psychological and activity-based interventions for cancer-related fatigue. Health Psychol 26:660-667, 2007
28. Myers J, Prakash M, Froelicher V, et al: Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 346:793-801, 2002
29. Sui X, LaMonte MJ, Laditka JN, et al: Cardiorespiratory fitness and adiposity as mortality predictors in older adults. JAMA 298:2507-2516, 2007
30. Visser M, Goodpaster BH, Kritchevsky SB, et al: Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 60:324-333, 2005
31. Courneya KS, Segal RJ, Mackey JR, et al: Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. J Clin Oncol 25:4396-4404, 2007
32. Ohira T, Schmitz KH, Ahmed RL, et al: Effects of weight training on quality of life in recent breast cancer survivors: The Weight Training for Breast Cancer Survivors (WTBS) study. Cancer 106:2076-2083, 2006
33. Hewitt M, Rowland JH, Yancik R: Cancer survivors in the United States: Age, health, and disability. J Gerontol A Biol Sci Med Sci 58:82-91, 2003
34. Sweeney C, Schmitz KH, Lazovich D, et al: Functional limitations in elderly female cancer survivors. J Natl Cancer Inst 98:521-529, 2006

