Effects of Physical Activity on the Fatigue and Psychologic Status of Cancer Patients during Chemotherapy

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BACKGROUND. Fatigue is a common and often severe problem in cancer patients undergoing chemotherapy. The authors postulated that physical activity training can reduce the intensity of fatigue in this group of patients.

METHODS. A group of cancer patients receiving high dose chemotherapy followed by autologous peripheral blood stem cell transplantation (training group; n = 27) followed an exercise program during hospitalization. The program was comprised of biking on an ergometer in the supine position following an interval training pattern for 30 minutes daily. Patients in the control group (n = 32) did not train. Psychologic distress was assessed at hospital admission and discharge with the Profile of Mood States and Symptom Check List 90.

RESULTS. By the time of hospital discharge, fatigue and somatic complaints had increased significantly in the control group (P for both < 0.01) but not in the training group. Furthermore, by the time of hospital discharge, the training group had a significant improvement in several scores of psychologic distress (obsessive-compulsive traits, fear, interpersonal sensitivity, and phobic anxiety) (P value for all scores < 0.05); this outcome was not observed in the control group.

CONCLUSIONS. The current study found that aerobic exercise can reduce fatigue and improve psychologic distress in cancer patients undergoing chemotherapy. ***Cancer*** **1999;85:2273–7.** *© 1999 American Cancer Society.*

KEYWORDS: exercise, fatigue, mood, high dose chemotherapy, peripheral blood stem cell transplantation.

Fatigue is one of the most frequent side effects of cancer treatment. According to several studies, this symptom affects up to 70% of patients during chemotherapy and radiotherapy.[1-3] For many cancer patients, treatment-related fatigue is severe and imposes limitations on normal daily activities. Furthermore, this symptom can affect the course of treatment; indeed, fatigue is a dose-limiting symptom for some cancer therapies (e.g., those with interferon or interleukin-2). Nonetheless, up to 30% of cancer survivors have been reported to experience a loss of stamina for years after the cessation of treatment.[4-6] The causes of this problem are not understood completely; however, the origin of chronic fatigue most likely is multifactorial and includes physiologic, psychologic, and social components.[7]

Impairment of physical performance figures among the most important etiologic factors of chemotherapy-related fatigue. Cardiorespiratory and muscular deconditioning and chemotherapy-induced anemia can reduce work capacity; therefore, patients require a higher degree of effort to perform their usual activities. The resulting increments in metabolic rate and energy consumption produce tiredness and fatigue even

with normal daily activities. To reduce fatigue, patients may avoid physical exertion and down-regulate their level of activity. The resulting physical inactivity induces muscular wasting and can produce further loss of performance. Lowering endurance thus creates a self-perpetuating condition: diminished activity leads to easy fatigability and vice versa.[7]

Aerobic exercise (defined as the rhythmic contraction and relaxation of large muscle masses over an extended time) has been shown to improve physical performance in cancer patients.[8-11] In recent studies we observed a reduction in the fatigue reported by cancer patients after participation in an aerobic training program designed to improve physical performance.[9,11,12] However, the lack of an objective assessment of fatigue made an exact interpretation of our observations difficult.

In view of these considerations, we investigated the effects of an exercise program on the psychologic distress of cancer patients undergoing high dose chemotherapy (HDC).

PATIENTS AND METHODS

A successive series of 63 cancer patients with solid tumors or lymphomas were enrolled for participation in the study. Inclusion criteria were: age 18–60 years; active malignancy confirmed histologically; absence of associated psychiatric, muscular, cardiovascular, or pulmonary disease; and ability to understand written German. All patients had been selected for HDC followed by peripheral stem cell transplantation. The study was approved by the Ethical Commission of the University of Freiburg and informed consent was obtained from all participants.

In the week preceding HDC, all patients underwent a cardiologic examination (electrocardiogram [ECG], stress ECG, and echocardiogram). One patient showed abnormalities on the ECG and was excluded from the study. Overall, 62 patients fulfilled all requirements for participation in the study. Prior to the initiation of chemotherapy, patients were assigned to a training group (n = 29) or a control group (n = 33) according to the datum of hospitalization (patients recruited in odd weeks were included in the training group and patients recruited in the even weeks were included in the control group).

Psychologic status was assessed with two questionnaires, the short version of the Profile of Mood Status (POMS) [13,14] and the Symptom Check List (SCL-90-R).[15,16] These instruments are comprised of statements regarding subjective experiences and allow an assessment of affective states during the last week (in the case of the SCL-90-R) or the present day (in the case of the POMS). The short version of the POMS yields separate subscale scores for depression, fatigue, anger/hostility, and vigor. Similarly, the SCL-90-R yields a global severity index (positive symptoms distress index [PSD]) and separate subscales for somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism. Higher PSD scores indicate greater overall mood disturbance; lower vigor scores and higher scores for the remaining subscales indicate a higher intensity of disturbance in the examined areas. These instruments have been used in several clinical studies to evaluate affective states and mental symptomatology in different patient populations and have shown high reliability and validity.

Patients with solid tumors underwent HDC with cumulative doses of etoposide, 1.5 g/m^2; ifosfamide, 12 g/m^2; and carboplatin, 750–1500 mg/m^2 (n = 40); 5 patients also received epirubicin, 150 mg/m^2. Therapy for 1 patient in the control group was comprised of thiotepa, 500 mg/m^2; cyclophosphamide, 6 g/m^2; and carboplatin, 800 mg/m^2. One patient in the training group refused to complete chemotherapy and received the full dose of etoposide and only 67% of the planned doses of ifosfamide and carboplatin. Patients with lymphoma received cumulative doses of busulfan, 14 mg/m^2, plus cyclophosphamide, 60 mg/m^2 (n = 10) or carmustine, 300 mg/m^2; cytosine arabinoside, 1600 mg/m^2; etoposide, 800 mg/m^2; and melphalan, 140 mg/m^2 (n = 6). After chemotherapy all patients received peripheral autologous stem cell transplantation and daily subcutaneous injections of granulocyte-colony stimulating factor at a dose of 5 μg/kg body weight/day during neutropenia (absolute neutrophil count$< 0.5 \times 10^9$/L).

Patients in the training group performed a daily program of aerobic exercise comprised of "biking" with a bed ergometer (Rotomed; Reck Machinenbau GmbH, Betzenweiler, Germany). This device allows the simulation of biking motion without the patient leaving the bed. The patients "biked" for 1 minute with an intensity sufficient to reach a heart rate equivalent to at least 50% of the cardiac reserve, calculated as 220 − age − resting heart rate.[17] The procedure was repeated 15 times with pauses of 1 minute between bouts; therefore, training was performed for a total of 30 minutes each day. The mean workload during the training program was 30 ± 5 watts (range, 20–40 watts). During training sessions patients were supervised continuously by instructed study personnel. The physical performance of patients changed during hospitalization as result of variations in clinical parameters (e.g., hemoglobin concentration, nutritional status, infections, etc.). Therefore, the pedaling speed was readjusted daily to achieve the goal heart rate and then kept constant within single training sessions (15

bouts). The daily pedaling frequency varied between 30–50 cycles/minute. To calculate the mean heart rate during a training session, the heart rate was assessed at the end of each 1-minute workload and added; heart rate during pauses was not considered.

Patients who were febrile (> 37.5 °C) or who had platelet counts $< 20 \times 10^9$/L were instructed to interrupt training. Patients with World Health Organization (WHO) Grade 1 and 2 infections and no other complications restarted training after the abatement of fever and continued until discharge, whereas patients with severe infections (WHO Grade 3) or multiple complications did not resume training. Two patients in the training group elected to abandon the study after the second training day for personal reasons. Nine patients (three in the training group and six in the control group) developed significant complications during hospitalization: severe infection (one patient in the training group and three in the control group), moderate infection combined with gastrointestinal toxicity (one patient in the control group), moderate infection followed by allergic reaction after platelet transfusion (one patient in the training group), and nephrotoxicity combined with infection (two patients in the control group and one patient in the training group).

On the day of discharge, a second evaluation of the patient's psychologic status was performed. One patient in the control group refused to complete the questionnaire and was excluded from the study.

Statistical Analysis

The study was performed following the "intention-to-treat" principle. Baseline data were compared with the Student *t* test. To evaluate the changes in psychologic distress during hospitalization, we compared data from the two groups at the time of hospital admission and at discharge with the two-tailed Wilcoxon matched pairs test. Statistical calculations were performed using Graph Pad Prism 3.0 for Windows, Graph Pad Software, San Diego, CA. A $P < 0.05$ was considered to show statistical significance. Data are shown as the mean ± the standard deviation and range (in brackets).

RESULTS

At the beginning of the study no differences in the baseline characteristics or psychologic stress between the two groups were observed (Table 1) (Fig. 1). Patients in the training group performed the exercise program for 82% ± 16% of the hospitalization days.

During hospitalization, patients in the training group showed significant improvement in the obsessive-compulsive traits ($P = 0.005$), anxiety ($P = 0.01$), interpersonal sensitivity ($P = 0.0004$), and phobic anxiety ($P = 0.02$) domains (Table 2). These changes resulted in a reduction in the global psychologic distress in the SCL-90-R ($P = 0.03$). No significant increment in fatigue was observed during hospitalization ($P = 0.28$). Patients in the control group showed significant increments in the fatigue and somatization scores ($P < 0.02$ and $P < 0.001$, respectively) and a reduction in vigor ($P = 0.05$) during hospitalization; no significant changes in the remaining scores were observed (Table 2).

TABLE 1
Baseline Characteristics of Patients Completing the Study

	Training group	Control group	*P* value
No. of patients	27	32	
Age (yrs) (range)	40 ± 11 (21–59)	40 ± 10 (20–56)	0.47
Gender	9 male, 18 female	13 male, 19 female	
Body mass index (range)	24.5 ± 3.8 (18–32)	23.6 ± 2.9 (19–32)	0.78
Retransfused stem cells 10^6/kg body weight (range)	4.6 ± 3.7 (1.3–12)	4.1 ± 2.7 (1.1–14.5)	0.61
Diagnosis			
Breast carcinoma	13	12	
Metastatic breast carcinoma	3	3	
Seminoma	3	3	
Sarcoma/adenocarcinoma	2		
Small cell lung carcinoma		4	
Hodgkin disease	2	5	
Non-Hodgkin lymphoma	4	5	
Chemotherapy			
VIC/CCT	20	19	
VIC-E	1	3	
BEAM	4	2	
Bu/Cy	2	8	

VIC/CCT: etoposide, ifosfamide, and carboplatin/thiotepa, cyclophosphamide, and carboplatin; VIC-E: etoposide, ifosfamide, carboplatin, and epirubicin; BEAM: carmustine, cytosine arabinoside, etoposide, and melphalan; Bu/Cy: busulfan and cyclophosphamide.

DISCUSSION

Loss of physical performance and fatigue are frequent problems of cancer patients undergoing chemotherapy. After discharge from the hospital, the majority of patients find it difficult to perform daily activities. Moreover, some patients may require weeks to months to regain their pretreatment level of fitness. This impairment in physical fitness is a substantial contributor to reduced quality of life in cancer patients.

We previously have observed improvements in emotional stability in cancer patients participating in a training program.[9,11] However, the lack of a systematic and objective evaluation of psychologic distress made an exact interpretation of this observation difficult. We believe the current study adds additional evidence of the beneficial effects of physical activity on the mental status of cancer patients undergoing chemotherapy.

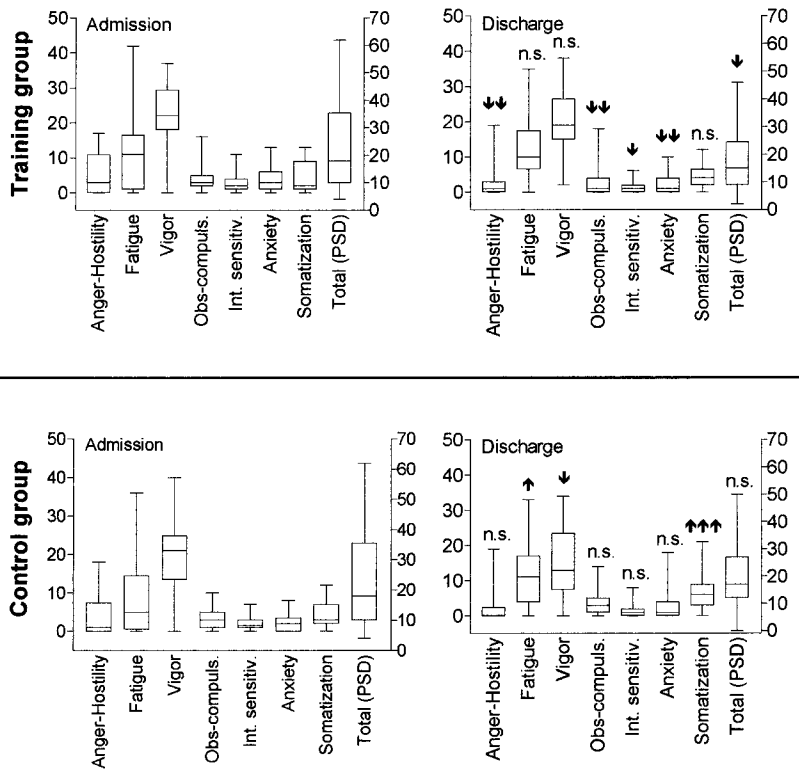

FIGURE 1. Scores in the Profile of Mood States (POMS) and the Symptoms Check List-90 (SCL-90-R) at hospital admission and at discharge. Scores were compared with the two-tailed Wilcoxon matched pairs test. Only domains showing differences between admission and discharge scores are shown. Obs-Compuls: obsessive-compulsive traits; Int. sensitiv: interpersonal sensitivity; ns: not significant ($P > 0.05$); ↑: increment; ↓: reduction; ↑, ↓: $P < 0.05$; ↑ ↑, ↓ ↓: $P < 0.01$; ↑ ↑ ↑, ↓ ↓ ↓: $P < 0.001$. The global severity index (positive symptoms distress index [PSD]) is shown on the right axis and all remnant scores are shown on the left axis.

Indeed, by the end of hospitalization, psychologic distress scores in several areas were reduced significantly in the training group whereas patients in the control group showed no improvement in mood state. Furthermore, the control group showed a significant increment in fatigue and somatization scores by the time of hospital discharge, an outcome not observed in the training group.

Several mechanisms may explain these results. Physical activity has been observed to improve symptoms of psychologic distress, particularly anxiety and depression, in patients with chronic diseases such as renal insufficiency,[18] ischemic heart disease,[19] and acquired immunodeficiency syndrome.[20] However, to our knowledge, the exact mechanisms underlying these observations have not been determined. Certainly the effects of physical activity are not limited to better cardiovascular or muscular function. Indeed, the improvement in physical performance can increase the feelings of control, independence, and self-esteem of patients; this improved self-confidence can result in better social interaction and a reduction in anxiety and fear. These mechanisms may explain the observed improvement in several indicators of psychologic distress (depression, anger/hostility, obsessive-compulsive traits, fear, interpersonal sensitivity, and phobic anxiety) observed in the training group. However, in our study, patients in the control group were not included in a structured program involving activities other than exertion; therefore, we cannot rule out possible nonspecific effects of attention or human contact on mood elevation. Further studies including placebo nonexercise activities for the control group are warranted to clarify this important question.

Conversely, the significant increment of fatigue during hospitalization observed in the control group suggests an organic etiology for this symptom in this setting. As mentioned earlier, the combined effects of chemotherapy and prolonged bed rest induce a substantial loss of physical performance. As result of the reduced work capacity, patients require a greater degree of effort to perform usual activities; the resulting increments in metabolic rate and energy consumption therefore produce tiredness and fatigue, even from normal activities. In a recent report we showed that aerobic training reduces the loss of physical performance in cancer patients undergoing HDC.[12] Consequently, these patients require a lower degree of effort to perform normal activities compared with their nontraining counterparts. As shown in the current study, this improvement in physical condition results in a reduction of fatigue during hospitalization.

Our results indicate that physical activity has beneficial effects on the mental status of cancer patients during chemotherapy. However, the current study included a small number of patients undergoing a particular treatment (HDC). Therefore, further studies are nec-

TABLE 2
Psychologic Status at Hospital Admission and at Hospital Discharge[a]

Training group	At admission	At discharge	*P* value
POMS			
Depression	12.8 ± 10.5 (0–35)	6.9 ± 10 (0–33)	0.11
Fatigue	9.6 ± 10.0 (0–42)	11.7 ± 8.9 (0–35)	0.28
Vigor	22.5 ± 8 (0–37)	19.6 ± 9 (2–38)	0.10
Anger/hostility	4.8 ± 5.7 (0–17)	2.7 ± 4.8 (0–19)	0.005
SCL-90-R			
Somatization	4.2 ± 4.1 (0–13)	4.3 ± 3 (0–12)	0.97
Obsessive-compulsive traits	3.8 ± 3.4 (0–16)	2.7 ± 3.8 (0–18)	0.005
Interpersonal sensitivity	2.7 ± 2.7 (0–11)	1.3 ± 1.5 (0–6)	0.004
Depression	5.5 ± 4.9 (0–21)	4.9 ± 4.6 (0–17)	0.51
Anxiety	3.4 ± 3.5 (0–13)	2 ± 2.5 (0–10)	0.01
Hostility	1.2 ± 1.5 (0–5)	0.9 ± 1.2 (0–5)	0.24
Phobic anxiety	1.7 ± 2.8 (0–13)	0.8 ± 1.3 (0–4)	0.02
Global psychologic distress	22.7 ± 14.9 (4–62)	17.7 ± 12.4 (2–46)	0.03
Control group	**At admission**	**At discharge**	***P* value**
POMS			
Depression	9.9 ± 9.6 (0–40)	6.2 ± 7.8 (0–34)	0.22
Fatigue	9.2 ± 10.2 (0–36)	11.5 ± 8.6 (0–33)	0.02
Vigor	19.9 ± 9.2 (0–40)	15.5 ± 9.8 (0–34)	0.05
Anger/hostility	3.7 ± 5.1 (0–18)	2.4 ± 4.7 (0–19)	0.21
SCL-90-R			
Somatization	4.1 ± 3.0 (0–12)	6.6 ± 5 (0–21)	0.001
Obsessive-compulsive traits	3.6 ± 2.9 (0–10)	3.7 ± 3.2 (0–14)	0.54
Interpersonal sensitivity	2.0 ± 1.7 (0–7)	1.5 ± 1.9 (0–8)	0.18
Depression	5.3 ± 3.7 (0–14)	6 ± 3.8 (0–14)	0.56
Anxiety	2.2 ± 2.3 (0–8)	3.0 ± 4.3 (0–18)	0.56
Hostility	1.3 ± 1.4 (0–6)	1.4 ± 2.3 (0–13)	0.60
Phobic anxiety	0.5 ± 1 (0–4)	0.6 ± 1.3 (0–5)	0.67
Global psychologic distress	19.6 ± 10.7 (3–43)	20.7 ± 11.4 (0–50)	0.68

POMS: Profile of Mood States; SCL-90-R: Revised Symptom Check List 90.

[a] Data are shown as mean ± the standard deviation with ranges in parentheses. Differences between scores at admission and discharge were compared with the Wilcoxon matched pairs test. Lower vigor score and higher scores in the remaining subscales indicate a higher intensity of disturbance in the examined areas.

essary to evaluate the effects of different programs of physical activity, including aerobic training and other forms of exercise, in patients with solid tumors and hematologic malignancies receiving conventional and intensified treatments. We have initiated further randomized studies addressing these important questions.

Aerobic training reduces treatment-related fatigue and improves the psychologic state of cancer patients receiving HDC.

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