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Prevention Strategies and Treatment of Fatigue in Cancer Patients

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Fatigue is a frequent and serious problem of patients with oncological and haematological diseases. Several studies have shown that this symptom may affect more than 60 percent of patients during therapy. Furthermore, fatigue may be a long-lasting problem and persist a long time after treatment. When the etiology of fatigue is identified, a causal therapy(i.e. blood transfusion or erythropoietin in patients with anaemia, antidepressants in patients with mood disorders) can be initiated. However, the genesis of fatigue is in the most cases multifactorial and includes psychological, physical and social factors.

Since the cause of fatigue in cancer patients is unknown, therapeutical approaches have been eclectic. A number of behavioral andpsychologic therapies (relaxation training, self-hypnosis, biofeedback, support groups) have been proposed for the treatment of cancer fatigue; however, no studies have evaluated the effects of these interventions in clinical settings. Pharmacological treatment of cancer fatigue has not shown positive or long-lasting results.

We have reported that fatigue may be related to the loss of physical performance experienced by cancer patients. In fact, cancer and treatment may generate several anatomical and functional changes(anaemia, reduction of vital capacity, impairment of left ventricular function, loss of muscle mass and of plasma volume, increased production of mediators of inflammation), which may result in a loss of physical performance. As a consequence of this, patients may be overwhelmed even by usual, low-intensity daily activities. For these patients, even light physical effort may cause dyspnea, tachycardia and muscle soreness. To reduce discomfort, patients are advised to avoid physical effort and to reduce the level of physical activity. However, the result of these empirical measures can be paradoxical. Cancer patients reduce the physical activity to a minimum and avoid usual activities like stair climbing or walking for prolonged periods. Thisresults in a lack of physical activity, which generates a severe loss of muscle mass and a further impairment of the cardiorespiratory function. Therefore, a self-perpetuating condition of easy tiredness, reduced activity and further impairment of physical performance is created.

In recent years, a growing interest has developed about the effects of endurance and resistance exercise in patients undergoing chemo- or radiotherapy. Several trials have consistently shown an improvement of the quality of life and of the physical performance and a reduction of fatigue in patients who carry out an exercise programme. Physical activity generates an increase of muscle mass and an improvement in cardiovascular capability; therefore, less effort is necessary in orderto manage the everyday activities. Nevertheless, the effects of exercise are not limited to an improved performance status or to a higher quality of life: endurance training has been shown to reduce the severity of secondary effects and to accelerate bone marrow regeneration after high-dose chemotherapy and stem cell rescue.

Other therapies for the treatment of fatigue have been evaluated recently. Individual and group psychotherapy and cognitive behavioural techniques may lead to a reduction of the fatigue in patients after chemotherapy. Moreover, this last method may be used to treat the mental fatigue in cancer patients. Further studies are needed to evaluate the effects of the above mentioned interventions in different populations of cancer patients and their benefits and disadvantages.

Effects of Aerobic Exercise on the Physical Performance and Incidence of Treatment-Related Complications After High-Dose Chemotherapy

By Fernando Dimeo, Sebastian Fetscher, Winand Lange, Roland Mertelsmann, and Joseph Keul

Loss of physical performance is a universal problem of cancer patients undergoing chemotherapy. We postulated that this impairment can be partially prevented by aerobic exercise. In a randomized study, 33 cancer patients receiving high-dose chemotherapy followed by autologous peripheral blood stem cell transplantation (training group, T) performed an exercise program consisting of biking on an ergometer in the supine position after an interval-training pattern for 30 minutes daily during hospitalization. Patients in the control group (C, n = 37) did not train. Maximal physical performance was assessed with a treadmill test by admission and discharge. Physical performance of the two groups was not different on admission. The decrement in performance during hospitalization was 27% greater in the control group than in the training group ($P = .05$); this resulted in a significantly higher maximal physical performance at discharge in the trained patients ($P = .04$). Duration of neutropenia ($P = .01$) and thrombopenia ($P = .06$), severity of diarrhea ($P = .04$), severity of pain ($P = .01$), and duration of hospitalization ($P = .03$) were reduced in the training group. We conclude that aerobic exercise can be safely carried out immediately after high-dose chemotherapy and can partially prevent loss of physical performance. Based on the potential significance of the observed outcomes, further studies are warranted to confirm our results.

FATIGUE AND IMPAIRMENT of physical performance are common, and sometimes serious, side effects of cancer treatment. It has been estimated that the problem affects up to 70% of cancer patients during chemotherapy or radiotherapy.[1-4] For many patients, particularly in the recovery phase immediately after treatment, low physical performance imposes limitations on basic daily activities. Postulated etiologic mechanisms for the development of this problem include impaired nutritional status, sleep disturbances, biochemical changes secondary to disease and treatment, psychosocial factors, and reduced level of activity.[5] However, the causes of impaired physical performance in this setting are not yet fully understood. One frequently underestimated factor contributing to loss of physical performance in cancer patients is the lack of muscular activity during in-hospital treatment. Inactivity inevitably results in muscular catabolism, producing rapid loss of performance. The deleterious effects of prolonged bedrest are well documented.[6-8]

Aerobic exercise (defined as the rhythmical contraction and relaxation of large muscle masses over an extended time) has been shown to improve physical performance and reduce fatigue in cancer patients.[9-12] However, this is not yet a widely accepted concept. Furthermore, some physicians fear that vigorous exertion may be harmful for cancer patients, although no literature reports support this notion.

We investigated the effects of aerobic exercise on the loss of physical performance and on the incidence and severity of complications in patients undergoing high-dose chemotherapy (HDC) followed by autologous peripheral blood stem cell transplantation (PBSCT).

MATERIALS AND METHODS

Eighty patients with solid tumors selected for treatment with HDC were considered for participation in the study. Inclusion criteria were the following: malignancy confirmed by biopsy; Eastern Cooperative Oncology Group (ECOG) performance score of 0-2; age between 18 and 60 years; no evidence of impairment of cardiac, pulmonary, renal, and hepatic function; absence of bony metastases in the lower extremities; and transplantation of at least 1×10^6 $CD34^+$ peripheral blood stem cells/kg body weight. The study was approved by the Ethics Committee of the University of Freiburg and informed consent was obtained from all patients. From the 80 potential participants, 72 (90%) fulfilled inclusion criteria and were enrolled in the study.

Before HDC, all patients received one to four chemotherapy cycles consisting of etoposide 500 mg/m^2, ifosfamide 4 g/m^2, cisplatinum 50 mg/m^2, with or without epirubicine 50 mg/m^2 (VIP/VIP-E), followed by administration of granulocyte colony-stimulating factor (G-CSF) at a dose of 5 μg/kg body weight/d. Ten days after the last cycle of chemotherapy, leukapheresis for collection of peripheral blood stem cells was performed. In the week before admission for HDC, all patients underwent a complete physical and cardiovascular examination (electrocardiogram [ECG] and echocardiogram). Two patients showed abnormalities on electrocardiography and were excluded from the study.

Overall, 70 patients fulfilled all requirements for participation (Table 1). On their first day of hospitalization, patients were assigned randomly to a training (T) or a control group (C). In the week preceding HDC, a treadmill stress-test under continuous ECG monitoring (starting at 3 km/h and 1.5% elevation, acceleration of 1 km/h every third minute by unchanged elevation and continued until exhaustion) was performed for assessment of physical performance. This stress-test is one of the standard protocols used in Germany for assessment of maximal physical performance of patients with reduced physical performance as sequel of chronic diseases and correlates highly with VO2max.[13,14] During the test patients were not allowed to hold handrails.

All patients underwent high-dose chemotherapy with cumulative doses of etoposide 1.5 g/m^2, ifosfamide 12 g/m^2, and carboplatin 750-1500 mg/m^2 (VIC, n = 57); 13 patients also received epirubicine, 150 mg/m^2 (VIC-E, n = 13). One patient in the training group refused to complete chemotherapy and received the full dose of etoposide and only 2/3 of the planed dose of ifosfamide and carboplatin. After chemotherapy all patients received autologous

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Submitted December 27, 1996; accepted July 7, 1997.

Supported by the Nenad Keul Foundation Preventive Medicine, Freiburg in Breisgau, Germany.

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0006-4971/97/9009-0036$3.00/0

Table 1. Baseline Characteristics of the Patients

	Training	Control	Significance of *P*
No.	33	37	
Age (yr)	39 ± 10	40 ± 11	.52
Gender	23 female, 10 male	28 female, 9 male	.75
Body-mass-index	25 ± 6	24 ± 4	.30
Diagnosis:			
Breast cancer	16	19	
Metastatic breast cancer	7	4	
Germ cell cancer	6	7	
Sarcoma	2	3	
Small cell lung carcinoma	—	1	
Non-small cell lung carcinoma	1	2	
Adenocarcinoma	1	—	
Neuroblastoma	—	1	
Chemotherapy:			
VIC	27 (81%)	30 (81%)	
VIC-E	6 (9%)	7 (9%)	
Mean no. of chemotherapy cycles preceding HDC	1.8 ± 0.4	1.8 ± 0.5	.65
Dose of carboplatin (mg)	429 ± 103	395 ± 100	.17
Retransfunded stem cells (10^6/kg body weight)	4.65 ± 3.5	3.90 ± 2.9	.34

Values are expressed as mean ± SD.

Complete blood counts and serum chemistry (including evaluation of hepatic and renal function) were carried out daily between 6:00 and 8:00 AM, ie, after at least 12 hours without training. Criterion for blood transfusion was hemoglobin concentration of less than 8 g/dL; criteria for platelet transfusion were thrombopenia $< 20 \times 10^9$/L or bleeding. Discharge criteria were trilinear hematopoietic reconstitution, transfusion independency, an afebrile period of at least 2 days after discontinuing intravenous antibiotics, resolution of mucositis, ability to tolerate solid food, and absence of clinical signs of fluid overload or dehydration.

On day of discharge, a second cardiologic examination consisting of an ECG, echocardiogram, and stress-test was carried out. By this time most patients were still recovering from chemotherapy-related mucositis and could not tolerate a mouthpiece for direct assessment of VO2max. Therefore, this parameter was not assessed. Instead, maximal physical performance was defined as the maximal speed (in kilometers per hour) reached in the treadmill stress-test. Because VO2max is a function of maximal walking speed,[14] these two parameters are intimately correlated.

Four patients in the control group (three patients refusing participation, another patient presenting with atrial fibrillation) and two patients in the training group (refusal of participation) did not undergo a second stress-test. Severity of chemotherapy-related complications of these six patients was included in the statistical analysis; however, data of their physical performance were not considered.

Hematologic and nonhematologic toxicity were analyzed according to standard WHO criteria.[15] These assessments were made by an investigator who was blinded to the patients' assignments to control and treatment group. Duration of hospitalization was mea-

Table 2. Physical Performance, Hematologic Values, and Secondary Effects of Chemotherapy in the Two Groups

	Training	Controls	Significance of *P*	95% CI
Hospital admission:				
Maximal performance (km/h)*	7.91 ± 1.2	7.51 ± 1.3	0.18	−0.18; 1.17
Maximal heart rate in the stress-test (bpm)	170 ± 18	168 ± 16	0.58	−6; 10
Percentage of estimated maximal heart rate (220 − age)	94 ± 7%	94 ± 8%	0.89	−3; 4
Hemoglobin concentration (g/dL)	10.5 ± 1.6	10.7 ± 1.3	0.50	−0.98; 0.48
Hematocrit	30 ± 4%	31 ± 4%	0.42	−2.96; 1.26
Discharge from hospital:				
Maximal performance (km/h)*	6.85 ± 1.1	6.08 ± 1.3	0.04 (1)	0.12; 1.41
Maximal heart rate in the stress-test (bpm)	166 ± 21	168 ± 19	0.84	−11; 9
Percentage of estimated maximal heart rate (220 − age)	92 ± 10%	93 ± 9%	0.69	−6; 4
Hemoglobin concentration (g/dL)	9.7 ± 0.9	9.5 ± 1.1	0.49	−0.31; 0.65
Hematocrit	27 ± 2%	27 ± 3%	0.71	−1.27; 1.72
Loss of physical performance during hospitalization (%)	14 ± 9%	19 ± 11%	0.05	−10.43; 0.20
Duration of neutropenia $<0.5 \times 10^9$/L (d)	6.6 ± 1.5	7.6 ± 1.6	0.01	−1.71; −0.16
Duration of thrombopenia $<50 \times 10^9$/L (d)	10.9 ± 3	12.4 ± 3.7	0.06	−3.14; 0.14
Blood transfusions (U)	3.3 ± 1.4	3.3 ± 2	0.92	−0.89; 0.82
Platelets transfusions (U)	19.5 ± 14.1	26.9 ± 19.5	0.06	−15.7; 0.8
In-hospital days	13.6 ± 2.2	15.2 ± 3.6	0.03	−3.07; −0.10
Severity of mucositis†	2.34 ± 0.8	2.43 ± 0.55	0.38	−0.42; 0.24
Severity of diarrhea†	1.90 ± 1	2.37 ± 0.86	0.04	−0.92; −0.01
Severity of infection†	2 ± 0.5	2.1 ± 0.39	0.33	−0.23; 0.47
Severity of pain†	1.87 ± 0.75	2.4 ± 0.49	0.01	−0.68; −0.56

* Data of 28 patients in the training and 32 patients in the control group who performed the stress-test before and after HDC; see text.
† According to the WHO scale. Values are expressed as mean ± SD and 95% confidence intervals for the difference between groups.

Patients in the training group performed the aerobic exercise program for 82% (±10%) of hospital days.

Physical performance. Maximum performance of both groups was not different at initiation of the study (see Table 2). Loss of performance during hospitalization was 27% higher in the control group than in the training group (absolute values: training group 14%, control group 19%, $P = .05$, resulting in a significant difference between the maximal performance of both groups at discharge ($P = .04$).

Hematological indexes. Hemoglobin concentration and hematocrit were not different between the groups at admission or discharge. The training group had a shorter duration of neutropenia (ANC $< 5 \times 10^9$/L, $P = .01$) and of thrombopenia (platelets $<50 \times 10^9$, $P = .06$, see Fig 1); the requirement for platelet transfusions was also lower in the training group ($P = .06$). Number of erythrocytes transfusions was not different for the two groups ($P = .92$).

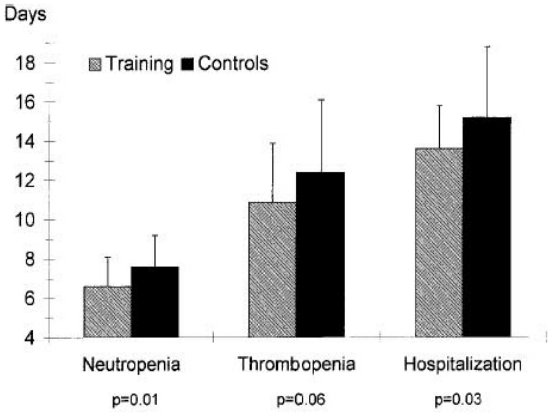

Fig 1. Duration of neutropenia (ANC $< 0.5 \times 10^9$/L), thrombopenia (platelets $<50 \times 10^9$/L), and hospitalization (calculated as days between stem cell reinfusion and discharge) for the training and control groups.

Cardiologic examinations. One patient in the control group developed atrial fibrillation shortly after HDC. For the remaining patients, ECG at rest and during stress-test, and echocardiographic assessment of cardiac dimensions and function (heart volume, HV and shortening fraction, SF) showed no changes between the two examinations (by admission: T: HV 733 ± 134 mL, SF 37% ± 4%, C: HV 733 ± 140 mL, SF 38% ± 5%; at discharge: T: HV 713 ± 128 mL, SF 36% ± 4%; C: HV 720 ± 143 mL, SF 37% ± 6%).

Toxicity of HDC. Fifteen patients (21%) developed significant complications: severe infection (4 patients in the training group, 5 controls), moderate infection combined with diarrhea (1 patient in each group), hepatic hemorrhage (1 patient in the training group), atrial fibrillation (1 patient in the control group), chemotherapy-related seizures (1 control), and moderate infection followed by allergic reaction after platelet transfusion (1 patient in the training group). Severity of mucositis was not different for the two groups (Fig 2). The incidence of diarrhea was lower in the training group ($P = .04$). Severity of pain was for patients in the training group lower than for control patients ($P = .01$). No patient in the training or control group developed signs of renal toxicity. One patient in the training group died of hepatic hemorrhage on the fourth day after PBSCT. Severe intraabdominal bleeding necessitated laparotomy, which showed liver necrosis. This complication is a well-known

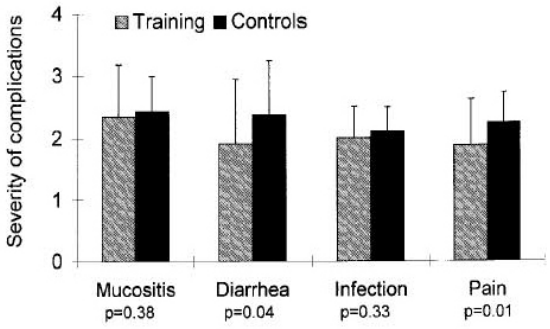

Fig 2. Intensity of complications after HDC according to WHO criteria.

DISCUSSION

Loss of physical performance and fatigue are a universal phenomenon in cancer patients after myelotoxic chemotherapy. After discharge, most patients find it difficult to perform daily activities. Moreover, some patients may need weeks or months to regain their pretreatment level of fitness.[2] Our study shows that the severe loss of performance regularly observed after HDC can be at least partially prevented with adequate rehabilitative measures. Our results also indicate that starting rehabilitation immediately after completion of HDC is possible without increasing morbidity.

Moreover, several positive outcomes were observed in patients who performed aerobic training during hospitalization. Firstly, duration of neutropenia in the training group was significantly shorter than for controls. Because neutro-

substantially higher percentage of patients in the control group required treatment with opioid analgesics (training group 4 patients, 12%; control group 10 patients, 27%). Literature reports offer an explanation for this finding. In several studies, physical exercise has been shown to elevate pain threshold[17-19]; the mechanisms proposed to underlie this effect are an activation of central pain inhibitory systems and a higher production of endorphins.[20]

Average duration of hospitalization was shorter for the training group than for controls. Because the decision to discharge a patient is made by the medical team based on clinical considerations, we cannot exclude that subjective factors affected this outcome. However, several objective parameters that also influence duration of hospitalization showed differences between the training and control groups. Furthermore, the medical staff was not informed about the secondary endpoints of the study. Therefore, the shorter duration of hospitalization for the training group may not entirely be an artifact because of subjective decisions made by the medical staff.

A critical point in our study was the comparability of effort of patients in the training and control groups during both stress-tests. To analyze this point, we compared the percentage of maximal predicted heart rate (220 minus age) reached by participants in the study in the stress-tests. No differences were found between the training and control groups (Table 2). These results indicate a comparable degree of effort in the two groups by all tests. Moreover, mean heart rate in all tests was more than 90% of the maximal predicted heart rate, indicating that the tests were performed until exhaustion and were not prematurely interrupted due to factors like coordinatory problems or pain.[14]

Echocardiography, resting, and exercise ECG showed no pathological changes in the training group at final testing. Furthermore, no patient in the training group developed clinical signs of cardiotoxicity during the 2 months after chemotherapy. This indicates that patients with no signs of impaired cardiac function can perform aerobic exercise after HDC with the described protocol and autologous PBSCT without fear of cardiac complications.

In the present study we have furnished evidence that aerobic exercise may be useful in preventing the loss of physical performance in cancer patients after myelotoxic chemotherapy. Furthermore, these data, while limited, suggest that exercise can be performed safely after HDC and PBSCT. Likewise, our finding of reduced chemotherapy-related complications in trained subjects is provocative. Clearly, all of these findings require confirmation. A randomized prospective study including patients with hematologic malignancies undergoing autologous and allogeneic bone marrow transplantation has been initiated to address this question.

ACKNOWLEDGMENT

The authors thank the doctoral students Annette Hahn, Ulrike Augustin, Murad Ruf, and Christoph Janzen, who supervised the patients during the study; Dominik Grathwohl for his advice concerning statistics; and Monika Tilmann, MD, and Ralf Beneke, MD, for revision of the manuscript and many helpful suggestions.

REFERENCES

1. Irvine DM, Vincent L, Graydon J, Bubela N, Thompson L: The prevalence and correlates of fatigue in patients receiving treatment with chemotherapy and radiotherapy. A comparison with fatigue experienced by healthy individuals. Cancer Nurs 17:367, 1994

2. Smets EMA, Garssen B, Schuster-Uitterhöve ALJ, de Haes JCJM: Fatigue in cancer patients. Br J Cancer 68:220, 1993

3. Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D: Psychosocial problems among survivals of Hodgkin's disease. J Clin Oncol 4:805, 1986

4. Cassileth BR, Kusj EJ, Bodenheimer BJ, Farber JM, Jochimsen P, Morin-Taylor B: Chemotherapeutic toxicity—The relationship between patients expectations and post-treatments results. Am J Clin Oncol 8:419, 1985

5. Winningham ML, Nail LM, Barton Burke M, Brophy L, Cimprich B, Jones LS, Pickard-Holley S, Rhodes V, St Pierre B, Beck S, Glass EC, Mock V, Mooney KH, Piper B: Fatigue and the cancer experience: The state of the knowledge. Oncol Nurse Forum 21:23, 1994

6. Greenleaf J, Kozlowsky S: Physiological consequences of reduced physical activity during bed rest, in Terjung R (ed): Exercise and Sports Science Review. Philadelphia, PA, Franklin Institute Press, 1982, p 84

7. Hinterbuchner C: Rehabilitation of physical dysability in cancer. NY State J Med 78:1066, 1978

8. Christensen T, Stage JG, Galbo H, Christensen J, Kehlet H: Fatigue and cardiac and endocrine metabolic response to exercise after abdominal surgery. Surgery 105:46, 1989

9. Winningham ML, MacVicar MG: Effects of aerobic interval training on cancer patients functional capacity. Nurs Res 38:348, 1989

10. Dimeo F, Bertz H, Finke J, Mertelsmann R, Keul J: A rehabilitation program for patients with haematological malignancies undergoing bone marrow transplantation. Bone Marrow Transplant 18:1157, 1996

11. Dimeo F, Tilmann M, Bertz H, Kanz L, Mertelsmann R, Keul J: Aerobic exercise in the rehabilitation of cancer patients undergoing high dose chemotherapy and peripheral stem cell transplantation. Cancer 79:1717, 1997

12. Dimeo F, Rumberger BG, Keul J, Mertelsmann R: Aerobic exercise as therapy for cancer fatigue. Med Sci Sport Exer (in press)

13. Hollman W, Hettinger T: Sportmedizin: Arbeits- und Trainingsgrundlagen (ed 3). Stuttgart, Germany, Schattauer, 1990, p 392

14. American College of Sports Medicine: Guidelines for Exercise Testing and Prescription (ed 3). Philadelphia, PA, Lea & Feibiger, 1995

15. WHO Handbook for Reporting the Results of Cancer Treatment. Geneva, Switzerland, WHO, 1979, p 41

16. Nieman DC, Nehlsen-Cannarella SL: The immune response to exercise. Semin Hematol 31:166, 1994

17. Varrassi G, Bazzano C, Edwards WT: Effects of physical activity on maternal plasma beta-endorphin levels and perception of labor pain. Am J Obstet Gynecol 160:707, 1989

18. Gurevich M, Kohn PM, Davis C: Exercise induced analgesia and the role of reactivity in pain sensitivity J Sports Sci 12:549, 1994

19. Fuller AK, Robinson ME: A test of exercise analgesia using signal detection theory and a within-subjects design. Percept Mot Skills 76 (3 Pt 2):1299, 1993 (suppl)

20. Droste C: Transient hypoalgesia under physical exercise: Relation to silent ischaemia and implications for cardiac rehabilitation. Ann Acad Med Singapore 21:23, 1992