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The effects of a six-week supervised multimodal exercise intervention during chemotherapy on cancer-related fatigue

Christina Andersen [a,*], Mikael Rørth [b], Bent Ejlertsen [b], Maria Stage [a], Tom Møller [a], Julie Midtgaard [a], Morten Quist [a], Kira Bloomquist [a], Lis Adamsen [a,c]

[a] The University Hospital Centre for Nursing and Care Research (UCSF), Department 9701, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[b] Department of Oncology, Copenhagen University Hospital, Blegdamsvej 9, DK-2100 Copenhagen, Denmark
[c] Copenhagen University Institute of Public Health, DK-1014 Copenhagen, Denmark

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A B S T R A C T

Purpose: Cancer related fatigue (CRF) is a common problem for cancer patients across diagnoses during chemotherapy and is associated with physical inactivity, lower functional level and lack of energy. Few RCT exercise intervention studies have included cancer patients undergoing chemotherapy. The objective of this study is to evaluate whether a six-week supervised multimodal exercise intervention, adjunct to chemotherapy and standard care, can reduce the patient's CRF level.
Methods: Data is based on analyses of a prospective randomised controlled trial 'The Body & Cancer Trial'. 213 cancer patients with different diagnoses were randomised into an intervention group or wait-list control group. The primary outcome, Fatigue score (CRF), was evaluated by the Functional Assessment of Cancer Therapy-Anaemia Questionnaire (FACT-An-) (FACT-G score & FACT-An Anemia subscale). Intervention: Supervised exercise, comprising high-intensity cardiovascular and heavy resistance training, relaxation- and body awareness training and massage, 9 h weekly for 6 weeks.
Results: CRF was significantly reduced in the intervention group, corresponding to a Fatigue score reduction of 3.04 (effect size of 0.44, 95% CI 0.17−0.72) ($P = .002$), the FACT-An score by 5.40 ($P = .015$), the FACT-An Toi score by 5.22 ($P = .009$) and the Anaemia-ANS by 3.76 ($P = .002$). There was no statistically significant effect on the General Quality of Life score (FACT-G) or on any of the individual wellbeing scores; Physical ($P = .13$), Emotional ($P = .87$), Social ($P = .83$) and Functional ($P = .26$).
Conclusion: In summary, this six-week supervised multimodal exercise intervention can lead to significant reduction in self-reported CRF in cancer patients undergoing chemotherapy.

Introduction

Cancer Related Fatigue (CRF) is a common complaint of cancer patients undergoing chemotherapy and is associated with the disease itself and with the antineoplastic treatment (Morrow et al., 2002; Hofman et al., 2007; Henry et al., 2008). The term CRF refers to a consistent burdensome feeling of physical, psychological and/or cognitive tiredness that affects the patient's functional level and is not relieved by rest or sleep (Mock et al., 2000). CRF is associated with physical inactivity, a lower functional level and lack of energy (Ahlberg et al., 2003; Lucia et al., 2003; Wagner and Cella, 2004). The prevalence of CRF in patients undergoing chemotherapy has been reported as being as high as 90% in the weeks following treatment (Morrow et al., 2002; Stasi et al., 2003; Hartvig et al., 2006).

The focus of the present study is the cancer patient's experience of fatigue while undergoing chemotherapy and participating in a multimodal exercise intervention. Attempts to prevent and treat CRF with drugs have not been successful (Minton et al., 2010; Campos et al., 2011). Inconsistent results are reported in systematic reviews and meta-analyses of randomized controlled trials (RCTs) of the physical exercise intervention effect on CRF in cancer patients during treatment (chemotherapy, radiation or hormonal therapy or a combination). Some meta − analyses (Cramp and Daniel, 2008; Kangas et al., 2008; Velthuis et al., 2010) have found significant positive effect on patients' CRF while others (Markes et al., 2006; Jacobsen et al., 2007; Speck et al., 2010) have found no statistical significant effects on CRF during treatment. Cancer patients undergoing chemotherapy can benefit from exercise interventions as evidenced by increased physical capacity (VO_2

* Corresponding author. Tel.: +45 3545 7388; fax: +45 3545 7399.
E-mail addresses: cia@rh.regionh.dk, ucsf@ucsf.dk (C. Andersen).

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max) (primary outcome) (MacVicar et al., 1989; Dimeo et al., 1997; Courneya et al., 2007; Schwartz et al., 2007; Quist et al., 2011). However, few exercise intervention studies in cancer patients undergoing chemotherapy have investigated the intervention's impact specifically on CRF. Some of the studies include small samples of women with breast cancer undergoing adjuvant chemotherapy (Mock et al., 1994; Schwartz, 1999; Schwartz et al., 2001; Yang et al., 2011) or haematological patients undergoing high-dose chemotherapy (Dimeo et al., 1999; Chang et al., 2008; Battaglini et al., 2009; Jarden et al., 2009). The RCT exercise intervention studies have documented significant positive effects on CRF while undergoing chemotherapy (Dimeo et al., 1999; Coleman et al., 2003; Headley et al., 2004; Courneya et al., 2007, 2009; Chang et al., 2008) while other studies did not (Jarden et al., 2009; Dodd et al., 2010). Based on the results of a number of studies utilizing low intensity interventions, progressive muscle relaxation training, body-awareness training and massage have been recommended as a concomitant intervention to relieve side-effects and symptoms such as fatigue in patients undergoing chemotherapy (Berger et al., 2002; Post-White et al., 2003; Demiralp et al., 2010). A recent RCT study by Sawada et al. (2010) investigated 24 weekly relaxation sessions (visualization and acupuncture) in patients undergoing chemotherapy ($n = 75$) and found statistically significant effect on fatigue in favour of the intervention group.

In the 'Body & Cancer' trial, we included cancer patients undergoing chemotherapy during the study period with different diagnosis. By combining five components (cardiovascular and heavy resistance training, relaxation, body awareness training, massage) we aimed to maximize the benefits of each of the components. The patients were randomized into an intervention group and a wait-list control group. The intervention was a supervised, multimodal exercise programme with high and low intensity, heavy resistance and cardiovascular components in addition to relaxation and body-awareness training and massage (Adamsen et al., 2006; Quist et al., 2006). We found positive effects of the intervention on depression (Midtgaard et al., 2011), aerobic capacity, muscular strength, physical and functional activity, vitality, emotional wellbeing and fatigue (Adamsen et al., 2009b).

The previous report on the "Body & Cancer" trial included fatigue measurement results using the European Organization for Research and Treatment of Cancer's Quality of Life Questionnaire (EORTC QLQ-C30) (3 items) and a small but clinically significant change was found (effect-size 0.33) (Adamsen et al., 2009b). The present report from the same trial concerns a more detailed, unpublished assessment of fatigue using the Danish version of the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire (fatigue 13 items) (Cella and Webster, 1997; Cella et al., 2002) and highlighting several dimensions of CRF.

The objective of this study is to evaluate whether a six-week supervised multimodal exercise intervention, adjunct to chemotherapy and standard care, can lead to a reduction in the patient's CRF level. Here we report the results when using the FACT-An questionnaire.

Methods

Participants

The study design of the '*Body & Cancer*' trial has been reported elsewhere (Adamsen et al., 2009b). Cancer patients were eligible to enter the study if they had received at least one cycle of chemotherapy for advanced disease or as adjuvant chemotherapy and were undergoing chemotherapy during the 6 week study period, had a WHO performance status of 0 or 1 and were between 18 and 65 years of age. Patients with brain or bone metastases, thrombocytopenia ($<50 \times 10^9$/l), myocardial infarction within the past three months or uncontrolled hypertension (diastolic pressure >95 mm Hg.) were excluded.

Randomisation and ethical considerations

After written informed consent and baseline measures were obtained, the patients were randomized by computer (Clinical Internet Trial Management System: CITMAS) to the intervention group or to the wait-list control group. The patients were stratified by gender, cancer diagnosis (breast, bowel, other solid tumours, haematological malignancies) and disease status (no evidence of disease or evidence of disease). Patients with No Evidence of Disease (NED) received adjuvant chemotherapy after radical local treatment for their cancer disease. Patients with Evidence of Disease (ED) had residual or advanced disease after the initial diagnosis of cancer was made by biopsy or local treatment. Participants assigned to the control group received conventional medical care and were allowed to undertake unrestricted physical activity and they completed outcome measures identical to those of the intervention group. The wait-list control group patients were invited to participate in the intervention programme after their participation in the six-week study. After the 6 weeks study period, 57% of the wait-list control group patients in this study subsequently elected to participate in the Body & Cancer intervention and as such it was not possible to report the follow-up data after the 6-week study period.

The study was approved by the Scientific Committees of the Copenhagen and Frederiksberg Municipalities (J.nr. 01-273/00) that evaluated both the ethical aspects and methodologies used in the research project. In addition, the study was approved by the Danish Data Protection Agency (J.nr. 2000-41-0-149).

The intervention: high- and low-intensity exercising

The intervention took place at a fitness facility located at the Copenhagen University Hospital and was carried out over a six-week period, 9 h weekly, in the morning (Monday, Tuesday, Wednesday, and Friday (Table 1). The patients trained in mixed groups (female and male) with seven to 10 participants per group. Each exercise session started with 30 min of warm-up exercises. The session ended with cool-down exercises consisting of dynamic exercises with the large muscle groups, stretching and coordination training.

The exercise intervention consisted of four high- and low-intensity activities: (1) *High-intensity physical training (heavy resistance – and cardiovascular training).* The fitness training involved 10-min. interval efforts on stationary bicycles, with an intensity of 85–95% of each patient's maximum heart rate. Warm-up and cool-down exercises comprised dynamic stretching actions with the large muscle groups, and coordination training (Saltin and Gollnick, 1983; Ainsworth et al., 2011); (2) *Relaxation training in groups.* The patients were instructed in the use of relaxation techniques, using principles of progressive relaxation when tensing and

Table 1
Multimodal exercise intervention, weekly schedule (values: hours).

	Monday	Tuesday	Wednesday	Thursday	Friday
High intensity training[a]	1.5		1.5		1.5
Low intensity training					
Body awareness		1.5			
Relaxation	0.5	0.5	0.5		0.5
Massage	0.5				0.5

[a] Comprising: warm-up exercises, heavy resistance and cardiovascular training.