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Randomized Control Trials

Effects of nutrition and physical exercise intervention in palliative cancer patients: A randomized controlled trial

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SUMMARY

Background & aims: Cancer cachexia is multifactorial and should be targeted using a multimodal form of intervention. The purpose of the present trial was to test the effects of a combined nutrition and physical exercise program on cancer patients with metastatic or locally advanced tumors of the gastrointestinal and lung tracts.

Methods: Patients were randomized into two groups: One group received a minimum of three standardized individual nutritional counselling sessions and participated in a 60-min exercise program twice a week. The second group received their usual care. The intervention spanned a period of three months. Quality of life (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire version 3.0), physical performance (hand-grip strength, 6-min walk test, timed sit-to-stand test and 1 repetition maximum leg press), nutritional status (body weight, bioelectrical impedance analysis), dietary intake (three-day dietary record) and clinical data (unexpected hospital days, performance status) were tested at baseline and after three and six months.

Results: In total, 18 women and 40 men (mean age 63, range 32–81) with metastatic or locally advanced tumors of the gastrointestinal ($n = 38$) and lung ($n = 20$) tracts were included. Median adherence to the supervised exercise program was 75%. The median number of individual nutritional counselling sessions was 3.0 (range 0–7 sessions). Post intervention, no difference in global health status/quality of life (overall QoL) was observed. Intervention was superior to UC for the patient-rated symptom scale regarding nausea and vomiting ($p = 0.023$) and protein intake ($p = 0.01$). No statistical differences were observed for energy intake, nutritional status and physical performance.

Conclusions: The results show good adherence to a combined nutrition and exercise program. The multimodal intervention did not improve overall QoL, but contributed to an adequate protein intake and to the general well-being of the patient by reducing nausea and vomiting.

1. Introduction

Anorexia, reduced physical functionality and metabolic abnormalities are common among palliative cancer patients and lead to persistent weight loss and loss of skeletal muscle mass [1,2]. Cancer-related weight loss and, eventually, cachexia, are associated with reduced tolerance and response to anticancer therapy, resulting in higher rates of hospital admission, increased in-hospital complications and prolonged hospital stays [3]. In patients with metastatic lung or gastrointestinal tumors, the prevalence of weight loss and its adverse effects are especially common [4].

Nutritional support remains the preferred strategy to prevent and treat cancer-related weight loss, despite the fact that nutrition as a single intervention practice has been investigated in advanced cancer patients with largely disappointing results [5]. Nutritional therapy improved dietary intake and some aspects of quality of life (QoL), but had no effect on nutritional, clinical and functional outcomes [6–8].

Recent studies therefore suggest earlier introduction of a multimodal approach to weight loss management in cancer patients [9]. There is persuasive evidence to assume that exercise

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and nutritional support forms a necessary component of such multimodal interventions: Nutritional counselling has been found to increase protein intake and, since cancer-related muscle atrophy is associated with a decreased responsiveness to various anabolic factors, physical exercise seems promising in stimulating anabolic metabolism and improving functional status [6,10]. When considered together, these data indicate that simultaneous nutrition and physical exercise intervention may act synergistically and improve nutritional and physical status and thereby QoL.

To our knowledge, data regarding the effects of combining nutritional support and physical exercise in patients with incurable cancer of the lung or of the gastrointestinal tract are still in short supply. The objective of the present randomized controlled trial was to investigate the effect of such a multimodal approach to therapy. The intervention group was assigned a three-month nutrition and physical exercise program, whereas the usual care group (control group) received their usual care. It was hypothesized that the multimodal intervention would improve physical performance and nutritional status and thereby positively affect QoL.

2. Patients and methods

The protocol of this single-center, two-arm, parallel group, randomized controlled trial was approved by the cantonal Ethics Committee Zurich (Switzerland) and registered at http://clinicaltrials.gov (NCT01540968). All patients were recruited from the cancer center at the Kantonsspital Winterthur and provided written informed consent.

2.1. Procedures

Cancer patients with metastatic or locally advanced tumors of the gastrointestinal or the lung tracts were eligible for inclusion if they had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of $\leq$2 [11] and a life expectancy greater than six months (as judged by the responsible physician). Patients were considered ineligible if they (i) were on enteral tube feeding or parenteral nutrition, (ii) had brain metastases or symptomatic bone metastases or (iii) had had an ileus within the last month. Inclusion into the study was not dependent on actual or planned tumor treatment.

The primary investigator (a food scientist with a master degree from the Swiss Federal Institute of Technology Zurich) enrolled patients and assigned them at a 1:1 ratio to either the intervention or the control group using randomly generated treatment allocations in sequentially numbered, sealed, opaque envelopes (block sizes of eight). Patients in the intervention group were assigned to the specially designed nutrition and physical exercise program (see below), whereas patients in the control group were treated according to the cancer center's standard medical therapy, following good clinical practice.

The treatment allocation was blinded from the primary investigator until completion of baseline assessment. No blinding of patients was used in group assignment. In addition, the provider of the physical exercise intervention and the dietician could not, by definition, be blinded. Blinding was used for data collection purposes only: a blinded physiotherapist assessed data on physical performance. Quality of life, nutritional status and dietary intake were assessed using questionnaires and devices. Clinical data were extracted from the most recent clinical records (+/−one week of the predetermined data).

2.2. Nutrition and physical intervention program

Within one week of the randomization, patients in the intervention group were enrolled in the three-month nutrition and physical exercise program.

2.2.1. Nutritional intervention

In total, there were a minimum of 3 nutritional counselling sessions planned within the intervention period (baseline, mid-intervention and end of intervention): The nutritional intervention comprised an extensive initial nutritional assessment followed by individual nutritional measures, i.e. enrichment of foods, energy and protein-rich snacks and oral nutritional supplements (ONS). The registered dietician assessed relevant aspects of the medical history (diagnosis, anti-cancer treatment, blood parameters, drugs and symptoms), usual and actual food intake, changes in body weight and relevant factors influencing dietary intake (appetite, chewing ability, capacity to swallow, dysgeusia, allergies and psychological factors). The main objective of the nutritional intervention was to enable patients to meet protein requirements (set at 1.2 g of protein per kg of actual body weight) [12]. The dietician also emphasized the potential benefit of protein-dense ONS consumption after physical activity. The protein-dense ONS contained 18–20 g protein in volumes ranging from 125 to 200 ml. The necessary energy intake was calculated according to the Harris–Benedict formula [13]. The patients' nutritional situations were reassessed after six weeks and three months after the baseline-assessment within the counselling sessions to adjust nutritional measures in the intervention group. The most important criteria determining whether nutritional counselling needed adjustment were dietary intake and body weight. If patients were not able to achieve protein and energy requirements and showed involuntary weight loss, further visits were arranged by the dietician throughout this period. To ensure reproducibility and consistency of individualized nutritional intervention, all patients in the nutritional therapy group were advised by the same dietician.

2.2.2. Physical intervention

The physical exercise program was conducted twice a week on the hospital's sporting premises. The exercise program was performed in groups of two to six patients and was supervised by an experienced physiotherapist. Each training session lasted 60 min and included defined warm-up exercises, strength and balance training exercises. The warm-up lasted 10 min and was conducted on a cycling ergometer (FREI SWISS AG, cycle 600 med). The strength program consisted of six machines covering the large muscle groups (arms, pectoral and abdominal muscles, lower back, thighs, and gluteal region) [14]. The six stations included leg press, leg flexion, pull down, abdominal trainer and bench press with a 10 kg barbell (FREI SWISS AG, active reha-systems). Only bench press was performed with free weights. The strength training was performed at 60–80% of one-repetition maximum capacity (1-RM) in two sets of 10 repetitions. The workload was adjusted at each session according to the individual fitness of the participant. The participants were instructed to increase resistance as soon as they were able to complete more than 10 repetitions.

Balance training was performed on a 1-cm Airex Balance mat (Airex TM; Aalen, Germany) and included (i) single leg stance, (ii) tandem stance, (iii) marching in place and (iii) heel raises [15]. The balance exercises were performed for both the left and right limbs, in a series spanning 1 min per move, increasing to 2 min as soon as the patient had progressed.

After each training session, the physiotherapist provided the protein-rich ONS to all study participants. Thus, the ONS were then consumed directly after each training session in the hospital.

2.3. Control group

The usual care group received the standard care of the cancer center: There was no type of exercise intervention offered to patients in the usual care group. Instead, they were asked to keep

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