Adherence to a Combined Exercise and Dietary Intervention in Patients With Gastrointestinal Cancer Undergoing Neo-adjuvant Therapy.

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Introduction

A high prevalence of patients with upper gastrointestinal (GI) cancer undergoing neo-adjuvant chemotherapy (ChT) experience dose limiting toxicity which may lead to a worse outcome. Factors associated with tolerance to ChT remain unclear, but it has recently been shown that alterations of body composition may play an important role. Body composition alterations such as sarcopenia and especially sarcopenic obesity have been related to higher ChT toxicity (Prado, et al., 2007) (Palmela, et al., 2017), increased post-op complications (Peng, et al., 2011) (Lieffers, Bathe, Fassbender, Winget, & Baracos, 2012) (Jolekar, Nau, & Mezhir, 2015) and lower overall survival (Martin, et al., 2013) (Kazemi-Bajestania, Mazurakb, & Baracos, 2016) (Chu, et al., 2017). Although, negative consequences of sarcopenia in cancer patients have been recognized, strategies focusing on improving/modifying body composition and whether these are able to modulate clinical outcome are still open to debate.

Dietary intake is a modifiable factor that seems to have an important role in skeletal muscle maintenance. It has been suggested that cancer patients may experience an anabolic resistance to protein stimuli, however protein synthesis is not completely blunted and may be responsive to an elevated protein intake. In fact, recent studies demonstrated that whey protein supplementation improved protein synthesis (Deutz, et al., 2011) and walking capacity (Gillis, et al., 2016) in cancer patients. Besides protein intake, the role of fat intake remains to be established. Most studies have focused on the effect of polyunsaturated fat intake, namely

n-3 polyunsaturated fatty acids which have demonstrated a beneficial effect in the treatment of age-related sarcopenia (Henderson, 2015) and cancer associated muscle wasting (Deutz, et al., 2011). However, in a study with cancer patients with advanced disease, fish oil was compared with olive oil as placebo and no difference was found (Bruera, et al.). It is also worth pointing out that dietary patterns may be more relevant than a single nutrient intake, and interestingly in a study conducted with older adults higher adhesion to Mediterranean diet (high intake of fruit, vegetables, olive oil, nuts, fish) was associated with a lower odds of sarcopenia (Hashemi, et al., 2015).

Exercise has been recently associated with improved functional capacity and better patient reported outcomes (quality of life and psychological outcomes) in cancer patients (Jones and Alfano 2013, Manja Idorna 2016). Although, only few studies have been conducted, there is already some evidence that exercise may improve functional capacity in several settings namely breast cancer patients receiving chemotherapy/radiotherapy (Jones and Alfano 2013), pre-surgery lung cancer (Jones and Alfano 2013) and incurable advanced disease (Oldervoll, Loge et al. 2011). In addition, operated breast cancer patients receiving adjuvant chemotherapy assigned to supervised resistance training were more likely to complete treatment (Jones and Alfano 2013). Still, there is limited information regarding the effect of exercise on body composition and outcomes such as post-operative complications, chemotherapy (ChT) response and toxicity.

It has also been hypothesized that exercise may inhibit tumor growth directly. In a recent experimental study, tumor bearing mice randomized to wheel running, showed a 60% reduction in tumor incidence across five different tumor models (Pedersen, et al.). Also, NK cell infiltration was significantly increased in tumors from running mice. Mechanistic analysis showed that NK cells were mobilized by epinephrine released during exercise, which resulted in a selective mobilization of IL-6 sensitive NK cells into the tumor. Another consequence of this mobilization of NK and other T cells, is to eventually sensitize and prime it to immunotherapy (Pedersen B. K., 2011).

Although an adequate dietary intake and exercise are suggested to improve body composition which may influence outcome, reported adherence to behavioral interventions has been showed to vary substantially. In a study that focused on evaluating the impact of exercise during and after treatments of recruited cancer patients from Radiation Oncology and Gynaecology department, adhesion to 3 and 6 month program of exercise was 93 and 91%, respectively (Grabenbauer, Grabenbauer, Lengenfelder, Grabenbauer, & Distel, 2016). Another

study aiming to explore the feasibility of dietary intervention focusing on a low-fat and high fruit and vegetable intake combined with moderate exercise in breast cancer patients, also found a high adherence (75%). However, according to a meta-analysis aiming at assessing adherence of colorectal adenoma patients to behavioral interventions such as diet and physical activity, a wide range of adherence was reported, 8 to 86 % and 13 to 47 %, respectively (McCahon, et al., 2015). Furthermore, in a feasibility study of exercise and diet interventions in pancreatic and lung cancer patients a suboptimal adhesion was reported, for exercise (60%), but especially for nutritional supplements (48%) (Solheim, et al., 2017).

Bearing in mind that adherence may be a limiting factor for randomized controlled trials investigating the effect of behavioral interventions, the purpose of our study is to conduct a study to investigate adherence of upper GI cancer patients to a combined exercise and dietary intervention.

General Aims:

- To study the adherence of upper GI cancer pts to a Combined Exercise and Diet Intervention (CEDI) during neoadjuvant chemotherapy.

Specific Aims:

- To determine the rate of completion of CEDI protocol.
- To analyze the proportion of participants which achieve ≥ 50% of dietary and exercise goals.
- To explore the effect of CEDI on ChT toxicity and post-op complications

Study design:

- Open label randomized controlled trial

Patient recruitment:

Recruitment will be conducted at the Oncology center of Hospital Beatriz Ângelo and patient selection will be done during the weekly multidisciplinary meeting. Patients will be enrolled at diagnosis of upper GI cancer, namely esophagus, gastric and pancreatic, provided that they are eligible for neoadjuvant ChT and with age higher than 18 years and lower than 80 years. Sample size per group was calculated bearing in mind that according to data form the World Health Organization, 14% of Portuguese adults are compliant to moderate exercise, and in our study adherence will be set as a compliance higher than 50%. Considering a power of 0.80 and an α set at 0.05, 25 patients will be needed per group. Stratified block randomization will be

conducted to allocate 25 patients to standard care and 25 to CEDI. Stratification will be performed according to disease location. Randomization will be undertaken by a randomization list created by a web based randomization system.

Methods:

- ***Clinical data:***

Demographic data such as age, sex, education level, drinking and smoking habits, and clinical data as tumor site and histological type, ChT regimens, response and toxicity, will be retrieved from electronic records. Adverse effects will also be recorded, namely ChT toxicitiy graded according to NCI Common Toxicity Criteria, and post -operative complications with Clavien Dindo classification.

- ***Patient Generated Subjective Global Assessment (PG-SGA)***

PG-SGA is known to be an accurate tool for the identification of malnourished cancer patients (Ottery F. , 1996) (Ottery F. , 1994). In our study, PG-SGA assessment will be conducted by an experienced dietitian and patients will be classified as well nourished (SGA A), moderately or suspected of being malnourished (SGA B) or severely malnourished (SGA C).

- ***Anthropometric measures (AM):***

AM have been used consistently due to their non-invasive feature, portability, and low cost (Rosa G, 2008). AM such as weight and height will be obtained, and Body Mass Index will be calculated. All AM will be conducted according to previously established protocols (Rosa G, 2008).

- ***Body composition assessment***

Body composition analysis will be conducted with CT scan image analysis. This technique is feasible since it is part of the clinical workup CD and GI cancer patients. CT methodology is highly precise to quantify specific tissues and to predict whole-body composition (Mourtzakis, Prado, Lieffers, Reiman, McCargar, & Baracos, 2008). Images will be acquired by Radiologists at the 3rd lumbar vertebra (L3) and processed with a specific software which performs a automatic segmentation of tissue cross-sectional areas. Manual corrections will be conducted by Radiologists, as necessary. Segmentation of tissue cross-sectional areas will be conducted according to the following Hounsfield unit (UH) thresholds: –29 to 150 for skeletal muscle, –190 to –30 for subcutaneous and intra-muscular adipose tissue and –50 to –150 for visceral

adipose tissue. Cross-sectional skeletal muscle, visceral fat and subcutaneous fat will be recorded in cm2 and mean muscle radiation attenuation in HU. Skeletal Muscle Index (SMI-cm2/height2) will also be calculated. Gender specific cut-offs for SMI will be used to define sarcopenia (Martin, et al., 2013).

BIA will also be performed since it is an objective, easy, portable and non-invasive technique (Kyle, et al., 2004). Several studies have used this methodology, and in particular phase angle has been investigated as a potential nutritional indicator (Gupta, et al., 2008). BIA will be performed using a bioelectrical impedance analyzer with dual frequency (5 and 50 kHz-Bodystat 1500 MDD, Bodystat Ltd, British Isles). BIA will be conducted with patients lying in a supine position with both hand and foot not touching the rest of the body. Measurements were taken on the right side of the body. Fat Free Mass, body fat, total body water, phase angle were recorded as well as raw data such as resistance and reactance.

- ***Dietary Intake assessment***

Dietary intake will be assessed with a Food frequency questionnaire and 24 recalls using a modified USDA five-pass method at diagnosis and every visit until surgery. The Semi-quantitative Food Frequency Questionnaire that will be used, was developed for the Portuguese population (Lopes, Aro, Azevedo, Ramos, & Barros, 2007) and is designed to evaluate usual dietary intake. This questionnaire includes 86 commonly-eaten food or drinks and participants were asked to estimate the amount and frequency of intake of each food/drink according to frequency and amount. Conversion of foodstuffs to nutrients will be conducted with software Food Processor Plus (ESHA Research, Salem, Oregon) which has been adapted to the Portuguese commonly-eaten food or drinks.

The 24h recall using a modified USDA five-pass method consists in 5 steps, the first is to list all foods consumed on the previous 24h. On the second step the interviewer asks about possible forgotten food items. In the third step the interviewer clarifies the time and occasion of the consumed foods. On the fourth step subject answers to standardized questions and clarifies portion size. In the last fifth step the interviewer seeks to obtain any additional information related to the foods consumed (Johnson & K, 2002). Conversion of foodstuffs to nutrients will be conducted with Sanut software which has been developed for the Portuguese population.

- ***Functional status assessment***

Performance Status will be assessed with Eastern Cooperative Oncology Group Performance Status scale (Oken, et al., 1982). According to these criteria patients are classified from grade 0

(fully active) to grade 4 (bedridden). Prior to initiation of ChT and before surgery, data on oxygen-consumption, optimum aerobic heart rate and ECG-recordings as well as 6 min walk test will be conducted. Also, hand held dynamometer assessing grip strength will be obtained. .

- ***Physical activity***

Physical activity will be assessed with the International Physical Activity questionnaire (Craig, Marshall, Sjostrom, Bauman, Booth, & Ainsworth, 2003). This questionnaire has been validated in several countries including Portugal, and is known to be a valid and reliable tool. Participants will be categorized has having a low, moderate or high physical activity according to the frequency, duration and intensity of physical activity on the previous seven days.

- ***Patient Reported Outcome Measures(PROMs)***

Quality of life questionnaires from the European Organization for Research and Treatment of Cancer (EORTC), specifically gastric, esophagus and pancreas modules, which have already been validated for the Portuguese population, will be used to asses Patient Reported Outcome Measures at the end of Chemotherapy treatment.

- ***Intervention arm-Combined Dietary and Exercise Intervention in the***

The intervention group will receive a supervised combined moderate aerobic and resistance training, once per week with duration of 40-60 min plus daily home exercise The exercise program will be planned by an exercise physiologist aiming at personalization of exercise according to patient's age and functional capacity.

Besides exercise, intervention group will receive a one-on-one nutritional counseling, by a Dietitian. In the first visit the dietary plan will be designed and oral nutritional supplements (Forticare®, Nutricia) will be recommended to meet 1.5g of protein/kg. Patients will be recommended to take one of the supplements after exercise. Also, in order to meet a calorie intake of 30kcal/kg, patients will be recommended to maintain a fat intake of 30% of total daily calories, where 20% will be supplied by olive oil. Written materials will be given to patients and caregivers, namely a dietary plan, standard menus, recipes, and standard portions information. Follow up visits will take place every time the patient is at the hospital to receive ChT .

Patients will be recommended to maintain the dietary plan and exercise during the whole ChT treatment plan. However, due to possible symptoms after ChT, namely nausea and vomitings, patients will be asked to intensify compliance on the week preceding ChT when there is a higher probability that patients are symptom free. Patients will be contacted twice a week by phone call or interview to provide motivation support and to assess if any diet or exercise

adjustment is needed in order to maximize adherence. Also an adhesion record will be provided to the patient for monitoring of adhesion to protein, olive oil, water, supplements intake as well as home exercise.

- ***Control arm- Standard care:***

Patients allocated to the control arm will receive standard care, in which patients will be referred to the dietitian only when the clinician feels there is a need for a dietary review. Whenever relevant, exercise will be recommended but without a personalized training program, which is our current practice.

- ***Adherence Assessment***

The primary outcome will be intervention adherence, in which patients consenting to engage in the intervention protocol will be evaluated. As a secondary outcome, we will assess to what extent participants achieve their dietary and exercise goals. Participants will be considered as adherent if they have met ≥ 50% of their diet and exercise goals on the week preceding ChT. Also, follow up rates will be recorded, as well as comments on burden and acceptability of the intervention. Dropout rates and reasons for leaving the study will also be recorded. Contamination of the control arm will also be analyzed. Patients will be contacted every week by phone call or interview to assess adherence.

Statistical analysis:

Statistical analysis will be conducted for the primary and secondary outcome with an intention to treat and per protocol approach, respectively. Continuous variables will be described as mean, median and range, while categorical variables will be expressed as frequency and percentage. Differences in mean continuous variables will be analyzed by t-test or Mann Whitney U test as appropriate, according to variable´s adjustment to a normal distribution. Shapiro-Wilk test will be used to test normality. Pearson or Spearman correlation analysis will be performed as appropriate to assess the association between continuous variables. Chi square test of independence or Fisher exact test will be used to assess the association between categorical variables.

Ethics:

The study protocol has been approved by the Scientific and Ethics Committee of Hospital Beatriz Ângelo in Loures, Portugal. Informed consent will be obtained from every patient.

Clinical data will be prospectively collected from electronic charts, however data will be coded in order to maintain anonymity.

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