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Study protocol

Oral Nutritional Supplementation for the Dietary Management of Malnutrition in Cancer: Study Protocol of A Randomized, Open-Label, Multicentre Clinical Trial

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Abstract

In cancer, more than 30% of patients die due to cachexia and more than 50% of patients with cancer die with cachexia being present. Patients with cancer cachexia frequently develop a chronic negative energy and protein balance driven by a combination of reduced food intake and metabolic change. Several studies have already demonstrated the usefulness of oral nutritional supplements (ONS) in managing malnutrition of cancer patients. Though increased energy intake is very important in managing cancer-related malnutrition, the source of this extra energy and the presence of anti-inflammatory and immunonutritional components may also play an important role. Here we present the study protocol of a randomized, open-label, multicentre clinical trial aimed to determine whether an ONS composed according to the needs of patients with malignant diseases an ONS composed according to the needs of patients with malignant diseases is more effective than a general product in improving the nutritional status in cancer patients.

Keywords: ***disease-related malnutrition, cancer, condition-specific oral nutritional supplement, clinical nutrition.***

Introduction

In cancer, more than 30% of patients die due to cachexia and more than 50% of patients with cancer die with cachexia being present.[1] Weight loss is also a major distress for cancer patients, partly because muscle wasting "makes the disease visible" and is taken as signifying the proximity of death. A systematic review found a negative relationship between loss of weight and health-related quality of life in cancer patients. Median overall survival (OS) was also significantly shorter in patients with pre-chemotherapy weight loss compared to those who had maintained their weight. Weight loss was associated with poor prognosis in several types of lung cancer.[2-5] Malnourished older patients with cancer may have an increased risk of early discontinuation of active antitumor treatment, which results in poor outcome in curative or adjuvant setting.[6]

Patients with cancer cachexia frequently develop a chronic negative energy and protein balance driven by a combination of reduced food intake and metabolic change.[7] However, the energy deficit alone does not explain the pathogenesis of cachexia seen in about half of all cancer patients. The presence of an acute phase response mediated by interleukins and tumor-derived factors, such as lipid mobilizing factor and proteolysis-inducing factor, has been linked to accelerated weight loss and a shortened survival time.[8]

Treatment for cachexia has concentrated on increasing food intake, although that alone is unable to reverse the metabolic changes.[9] Due to the hypercatabolic state and increased protein breakdown seen in malnourished / cachectic patients, increased energy and protein intake is vital in slowing down / stabilizing or even reversing weight loss and lean body mass /muscle wasting in cachectic patients.[10] While increased energy intake is very important in treating malnutrition / cachexia of patients with chronic diseases, the source of this extra energy also plays an important role in the therapy of the primary disease. Most malignant cells depend on steady glucose availability in the blood for their energy and biomass generating demands and are not able to metabolize significant amounts of fatty acids or ketone bodies due to mitochondrial dysfunction.[11] Moreover, many cancer patients exhibit an altered glucose metabolism characterized by insulin resistance.[12]

Several studies have already demonstrated the usefulness of oral nutritional supplements (ONS) in managing malnutrition of cancer

patients. However, no clinical trial has so far been published on comparing the effectiveness of different ONS with different compositions. Therefore, a randomized, open-label, multicentre clinical trial will be run to determine, whether an ONS composed according to the needs of patients with malignant diseases is more effective than a general product in improving the nutritional status in cancer patients.

Methods

Study design and participants

The study is designed as a randomized, open-label, multicentre clinical trial with an intervention (n=50) and a control group (n=50). Patients at or above the age of 18 years histologically confirmed, diagnosed within 2 months with locally advanced or metastatic cancer, with an ECOG 0-2 status will be enrolled into the study. Further inclusion criteria are the ability of consuming oral nutritional supplement, being managed by an outpatient clinic, life expectancy at least 6 months according to the treating physician, involuntary weight loss >5% in the past 6 months, or >2% when BMI<20 kg/m2. Exclusion criteria include pregnancy / breast-feeding, previous use of ONS ≥1.5 kcal/ml, proven intestinal obstruction, confirmed brain metastasis, co-morbidity with special dietary requirements (e.g. renal disease, diabetes mellitus), ascites, impaired hepatic functions (>2x ULN, in case of proven hepatic metastasis >5x ULN), acute or chronic renal failure (GFR<30ml/min), severe anaemia (Hgb <80 g/l), uncontrolled nausea and/or vomiting, use of megestrol-acetate and/or steroids that influence metabolism, use of any ONS and/or food supplement in the previous 3 months, known intolerance or allergy to any component of the interventional or control ONS, participation in any clinical trial within 30 days prior to the baseline visit.

Patients will be recruited in 3 oncology centres in Hungary. Study visits will be performed at baseline, month 1, month 2 and end of study at month 3. Body weight, body mass index (BMI), fat-free mass (FFM), upper arm circumference (UUC), serum C-reactive protein (CRP) and albumin levels, and quality of life based on the SF36 questionnaire will be measured at baseline. At the month 1 and month 2 visits, body weight, BMI, FFM, UUC, and adherence to the prescribed nutritional therapy, while at the end of study visit body weight, BMI, FFM, UUC, serum CRP and albumin, levels, quality of life, and adherence to the prescribed nutritional therapy will be determined. (Figure 1)

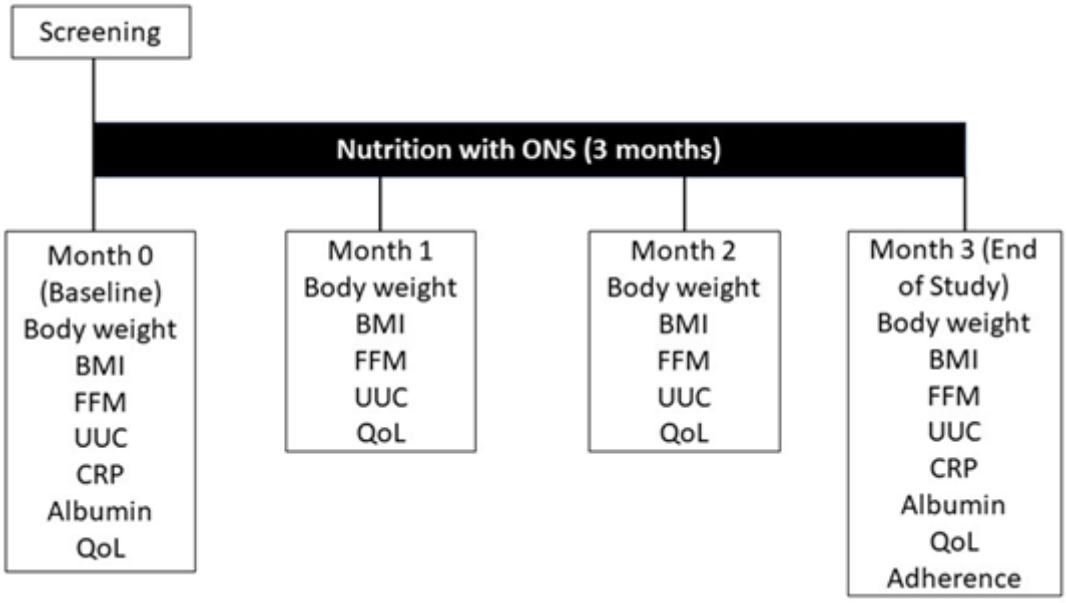

Figure 1: Flowchart of study procedures

The study has been approved by the National Public Health and Medical Officer Service. Written informed consent will be obtained from all participants.

Intervention

Patients will be randomized to a 3-month nutritional therapy with either an ONS designed for the dietary management of cancer-related malnutrition (interventional group, n=50), or an ONS recommended for the dietary management of disease-related malnutrition in general (control group, n=50). The individual prescribed dose of the interventional and the control ONS will be calculated based on the nutritional needs and the oral food intake of the patients. Adherence to the prescribed ONS will be determined by a registry card where the patient documents the ONS consumed each day. The registry card will be checked at each visit and patients will be advised to adhere to the nutritional therapy by the treating physician.

Randomisation

Patients will be randomised to either the interventional or the control ONS according to their order of appearance at the treating physician. Patients of Chinese origin will be, however, an exception: due to the rarity of such individuals in this patient population, they will be handled separately, and they will be enrolled into the interventional and the control group in an equal number in their order of appearance at the clinical trial site.

Outcomes

Primary outcome is the body weight change measured in kgs from baseline to the end of study (month 3). Secondary outcomes include change in BMI, FFM, upper arm circumference, and quality of life. Adherence will also be included among the secondary outcomes.

Sample size calculation

Sample size calculation was based on the magnitude of type I and II errors, the expected change in the body weight as the primary outcome, and the magnitude of standard error seen in previous clinical studies. The conventional 5% type I error and the 20% type

II error have been used in our clinical study ensuring a statistical power of 80%. The expected change in body weight that is able to influence the prognosis of the primary disease and the nutritional status of the patients has been determined as 3 kgs. A similar clinical trial[13] found that the magnitude of standard error of body weight change is 5-6 kgs. Based on these data, the number of patients need zo is included in each study group could be calculated according to the following formula:

$$n = \frac{2\left(Z_{\alpha} + Z_{1-\beta}\right)^{2\sigma^2}}{\Delta^2}$$

With a standard error of 5 kg, the number of patients in each study group would be 44, while with a standard error of 6 kg the number of patients in each study group would be 63. According to the practical considerations, the number of patients in both study groups will be 50.

Statistical analysis

Descriptive statistics will be used for the presentation of results: mean and standard error in case of continuous variables, and distribution in case of discrete variables. To perform the descriptive statistics-related hypothesis testing, parametric statistical probes, such as independent paired-sample t-test, one-way ANOVA in case of continuous variables, while χ^2 test and Fisher's exact test in case of discrete variables will be used. Regression analyses will be applied when multiple variables are concerned. The type of regression analysis will be defined based on the outcome tested (e.g. in case of survival-like data, Cox regression model will be used). The applicability criteria will be examined during the statistical hypothesis analyses.

Discussion

Malnutrition, anorexia and cachexia are common findings in cancer patients. Though they become more evident with tumor growth and spread, the mechanisms by which they are sustained often arise early in the history of cancer. For malnutrition, these mechanisms involve damage caused by the primary tumor or by specific anticancer therapies (surgery, chemotherapy, radiotherapy). This damage may arise also in cancers that usually are not directly responsible for nutritional and metabolic status alterations. For anorexia, meal-related neural or hormonal signals and humoral signals related to body fat or energy storage and the interaction of these signals with the hypothalamus or the inappropriate hypothalamic response play a pathogenic role.[14]

Higher energy intake attenuates the deterioration of the nutritional status,[15,16] significantly improves weight,[17] decreases the rate of complications,[18] may influence the modulators of the catabolic response,[19] has a sparing effect on protein utilization in order to favor restauration of lean body mass, and can improve the cancer patients' status and consequently their quality of life.[18]

Though increased energy intake is very important in treating malnutrition / cachexia of patients with chronic diseases, the source of this extra energy also plays an important role in the therapy of cancer. It is already well-known that most malignant cells depend on steady glucose availability in the blood for their energy and biomass generating demands and are not able to metabolize significant amounts of fatty acids or ketone bodies due to mitochondrial dysfunction. Moreover, high insulin and insulin-like growth factor 1 (IGF1) levels resulting from chronic ingestion of carbohydrate-rich Western diet meals, can directly promote tumor cell proliferation via the insulin / IGF1 signaling pathway. In addition, ketone bodies that are elevated when blood glucose and insulin levels are low, have been found to negatively affect proliferation of different malignant cells. Last but not least, many cancer patients exhibit an altered glucose metabolism characterized by insulin resistance. Thus, cancer patients may profit from a decreased carbohydrate and an increased protein and fat intake.[11]

While anorexia also may be present, the energy deficit alone does not explain the pathogenesis of cachexia seen in about half of all cancer patients. Some cytokines are also involved in the development of cachexia: the production of pro-inflammatory cytokines such as CRP, interleukin-6, proteolysis-inducing factor and lipid-mobilizing factor by tumor cells is the initial mechanism.[14] Diminishing the chronic inflammatory processes may also enhance the efficacy of the primary anti-tumor therapy and may ameliorate the quality of life of patients with malnutrition and cachexia.[20-24] Eicosapentaenoic acid (EPA) can reduce inflammation and has the potential to modulate nutritional status/body composition.[25] A diet rich in omega-3 fatty acids would negatively modulate the inflammatory cascade.[26]

L-carnitine, an endogenous mitochondrial membrane compound[27] with antioxidant effects has been found to be a protective agent against many diseases including cancer.[28] Since the levels of inflammatory cytokines as well as increased oxidative stress are related to cachexia, therapeutic strategies to ameliorate such conditions may be extremely important to counteract these deleterious effects. There is evidence that L-carnitine is able to reduce chronic inflammation and oxidative stress in cancer patients.

Dendritic cells, T and B lymphocytes, cytokines, antibodies, interleukins, and other molecules interacting with the immune system modulate a customized response against the cancer cell. Not only should patients' immune systems be unharmed, they must be strengthened by external agents, anti-tumor antibodies, immune checkpoint blockades, and cancer vaccines. Immunonutrition improves the immune and inflammatory systems via the modulation of their functional capacities by increasing the receptor densities on immune cell membranes and improving the ability to react against pathogens, maintaining CD4/CD8 lymphocytes and TNF alfa levels, and improving T cells and NK cytotoxicity functions.[29] The nutrients of immunonutrition formulas usually include arginine, omega-3 fatty acid, glutamine and RNA.

Our study is aimed to demonstrate that clinical nutrition with an ONS designed according to the special nutritional needs of malnourished cancer patients (high-energy-low-carbohydrate content, rich in immunonutrient components) may be more effective and may ensure higher adherence than nutrition of these patients with an ONS generally recommended for patients with disease-related malnutrition.

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Abbreviations:

ANOVA: analysis of variance,
BMI: body mass index,
CRP: C-reactive protein,
ECOG: Eastern Cooperative Oncology Group,
EPA: eicosapentaenoic acid,
EoS: end of study,
FFM: fat-free mass,
GFR: glomerular filtration rate,
Hgb: haemoglobin,
IGF1: insulin-like growth factor 1,
ONS: oral nutritional supplement,
OS: overall survival,
QoL: quality of life,
RNA: ribonucleic acid,
TNF: tumour necrosis factor,
ULN: upper limit of normal,
UUC: upper arm circumference