Research report

Nutrition therapy in cachectic cancer patients. The Tight Caloric Control (TiCaCo) pilot trial

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ABSTRACT

Background: Cancer is a common disease and many patients are diagnosed with advanced stages. Due to cancer generalization, patients may become ill-nourished and even cachectic. Malignancy-related cachexia is associated with worsening physical function, reduced tolerance to anticancer therapy and increased mortality. We assessed the effect of a patient-tailored nutritional approach in newly discovered, treatment-naive cancer patients with cachexia. Methods: In a randomized, single-blinded, controlled pilot study, patients were treated with either intensive, biometric parameter-oriented dietary counseling (nutrition therapy) compared to regular dietary counseling (control), before and during conventional cancer treatment. Twenty patients were enrolled over a one-year period, 10 receiving nutrition therapy and 10 controls. The primary endpoint was recovery of body composition after nutrition therapy. Secondary endpoints declined in morbidity and mortality with nutrition therapy. Results: Average weight evolution in the control group after 3, 6 and 12 months was 0.19 ± 7.87 kg, −9.78 ± 7.00 kg and −5.8 kg, and in the nutrition therapy group 0.69 ± 2.4 kg, 0.77 ± 2.58 kg and 1.29 ± 3.76 kg. Control patients had a significantly longer average hospital stay than subjects from the nutrition therapy group (37.6 vs. 3.4 days). Eight nutrition therapy patients and 1 control patient were still alive after 2 years. Conclusions: Nutrition therapy based on patient-specific biophysical parameters helps to maintain body weight and induces a more optimal nutritional balance in cachectic cancer patients. Moreover, survival in cancer patients improved when their nutritional status, even partially, ameliorated.

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Introduction

Cancer is an increasing medical problem worldwide. Many patients are still found to be incurable due to late detection of the disease. A major reason for this poor prognosis is an impaired nutritional status. This typically occurs in more advanced disease stages and is characterized by loss of appetite, nausea and vomiting (especially chemotherapy-induced), depression, loss of energy, and a hypercatabolic state due to an expanding or invasive tumor process. As a result, patients gradually weaken, become cachectic and finally die (Fearon, Arends, & Baracos, 2013). Therefore, restoring the nutritional status is gaining interest as an important supportive therapy for cancer. Restoring “nutritional health” indeed has been shown to beneficially influence morbidity and mortality (Rock et al., 2012).

The benefit of a healthy nutritional status during cancer treatment has been demonstrated in a wide variety of malignancies. Moreover, the nutritional status has an impact on cancer recurrence when a stable disease or complete remission is achieved. Dietary habits are also beneficial for prevention of some cancers in healthy individuals. Malignancies that may benefit from a more adequate nutrition policy are pancreatic (Pericleous, Rossi, Mandair, Whyand, & Caplin, 2014), breast (Chlebowski, 2013), head and neck (Langius et al., 2013), and lung cancer (Koutsokera, Kiagia, Saif, Soulitis, & Syrigos, 2013). The advantage is less obvious in other malignancies such as prostate cancer (Masko, Allott, & Freedland, 2013). For an in-depth description of the pathophysiology of

Abbreviations: CT, control treatment group; NT, nutrition therapy group.

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cancer-related cachexia, the reader is referred to the excellent review of Suzuki, Asakawa, Amitani, Nakamura, and Inui (2013).

A good nutritional status may largely influence the well-being of the patient and his/her environment (Lis, Gupta, Lamersfeld, Markman, & Vashi, 2012). Yet controversy exists on how to measure nutrition in combination with systemic anti-inflammatory treatment and erythropoietin improves survival in underweight patients (Wheelwright et al., 2013). A possible drawback of patient-centered dietary counseling may be the (in)ability of the patient to continue eating or following the diet. Focusing only on feeding without anticipating changes in physiological and psychological behavior is not appropriate. A holistic nutritional approach is imperative! Single nutritional supplements (e.g. addition of fish oil) do not offer much benefit (Ries et al., 2012). In contrast, optimal nutrition in combination with systemic anti-inflammatory treatment and erythropoietin improves survival in underweight patients with malignant disease (Lundholm, Daneryd, Bosaeus, Körner, & Lindholm, 2004).

Applying a previously established study design (Singer et al., 2011), we evaluated the effect of nutrition therapy on nutritional status, outcome, and survival of a broad population of cachectic cancer patients.

Materials and methods

Study design and patients

We conducted a randomized, controlled, single-blinded trial in the University Hospital Brussel (UZ Brussel), Belgium. The study was approved by the Institutional Review Board of the hospital and performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed consent was obtained from all patients.

Patients with a newly discovered histologically confirmed malignancy and in cachectic state were eligible for enrollment. Patients were included before the start of cancer treatment. The trial consisted of a screening period and a treatment phase. Follow-up extended up to 24 months after last patient enrollment. Evaluation was stopped in case of death, withdrawal of consent, or loss to follow-up.

Procedures

Tumor specifications, clinical and biological parameters, and baseline nutritional state (food intake, length, body weight and composition, basal and total energy expenditure) were assessed at enrollment. Energy expenditure was objectified by indirect calorimetry after an overnight fasting. Thereafter, physical activity and sleep efficiency were monitored with a validated device (SenseWear™ Armband (Cereda et al., 2007), BodyMedia, Pittsburgh, PA). Patients assigned to the control group received standard nutritional treatment under guidance of the oncology ward dietitian (i.e. counseling on importance of nutrition and general dietary advice) and were followed ambulatory thereafter.

The intervention group received a patient-specific dietary program that ensured that the caloric content of the proposed meals equaled their measured total energy expenditure. The recommended meals consisted of 30–35% fat (of which max. 10% saturated fat), 50–55% carbohydrates, 10–15% protein and adding at least 30 g of dietary fibers. It should be noted that the diet initially was individually designed depending on the patient’s dietary preferences, but adjusted if not implemented by the patient. Caloric and nitrogen intake were noted in a diary by the patient or his/her next-of-kin. In the intervention group, nutritional steps were taken when the caloric debt reached 5000 kcal. Interventions to correct an imbalance between nutritional intake and goals were included in climbing order: dietary adaptations or changes, oral supplements, enteral feeding through a feeding tube and parenteral nutrition. The interventional protocol was steered and coached by an “on call” dietitian and a physician from the hospital’s nutrition team. The evolution of all baseline variables was recorded at 3, 6, and 12 months.

Outcomes

The primary endpoints were preservation of body weight and restoration of the nutritional status. Secondary endpoints were morbidity and mortality. Morbidity was assessed by calculating the number of unexpected days of hospital stay corrected for treatment days. Overall survival was calculated from the day of study enrollment until time of death due to any cause. Patients alive at the time of analysis were censored (as their fate afterwards is unknown).

Statistical analysis

Statistical analysis was performed with GraphPad Prism 6. The Kaplan–Meier approach was used for estimating overall survival and corresponding two-sided 95% confidence interval for medians. Patients who were withdrawn or were lost to follow-up were censored at the date of last visit or at the last date of study medication, whichever occurred later. A Mantel–Cox test was used for survival analysis. Morbidity was assessed with a paired, two-tailed t-test.

Results

From January 2012 to August 2013, 64 patients were screened for eligibility. Finally, 20 subjects were enrolled over a one-year period. Ten patients (7 males) were entered in the nutrition therapy (NT) group. The remaining ten patients (6 males) formed the control (CT) group. Median age was 55.7 ± 9.2 years in the CT group and 61.4 ± 10.9 years in the NT group. Patients had a wide array of malignancies, with 8 subjects in each group having a TNM stage III or IV neoplasia. The median Karnofsky score was 90% in the NT and 85% in the CT group. Patients in both groups were studied for a median of 12 months. Median follow-up was 24 months. At the end of the study, no patients were receiving study-related treatment.

Baseline biophysical parameters and laboratory variables in both patient groups are presented in Supplementary Tables S1 and S2. The average body mass index (BMI) was 22.5 ± 5.2 kg/m² in the CT group and 22.1 ± 3.6 kg/m² in the NT group. The average weight was 68.0 ± 15.87 kg in the CT group, and 63.5 ± 9.71 kg in the NT group. Cancer types at randomization are given in Supplementary Table S3. Calorie intake and energy expenditure results (as measured by indirect calorimetry) can be found in Supplementary Table S4.

In the CT group, the average weight evolution after 3, 6, and 12 months was 0.19 ± 7.87 kg, -9.78 ± 7.00 kg and -5.8 kg, respectively. In the NT group, the average weight evolution after 3, 6, and 12 months was 0.69 ± 2.4 kg, 0.77 ± 2.58 kg and 1.29 ± 3.76 kg, respectively.

Cancers tended to respond better to treatment in the NT than in the CT group (6 vs.1 complete remission and 3 vs. 5 progressive diseases).

In both populations, median unexpected hospital stay was 37.6 days in the CT and 3.4 days in the NT group (95% CI –58.56–11.84, p = 0.0072) (Fig. 1). Median overall survival (OS) in the CT population was 8 months. Kaplan–Meier OS estimates were 4/10 patients at 12 months and 1/10 patients at 24 months. Median OS in the NT population was
undefined. Kaplan–Meier OS estimates were 10/10 patients at 12 months and 8/10 patients at 24 months (Fig. 2).

**Discussion**

We assessed the efficacy of a personalized interventional nutrition therapy protocol in cachectic patients with different types and/or stages of cancer. This approach resulted in a more optimal nutritional balance and a better maintained body weight. Moreover, patient-tailored nutrition improved morbidity and mortality. Treated patients had a significantly less longer duration of hospital stay.

A deplorable nutrition status or overt cachexia is correlated with worse prognosis in cancer patients. This was shown in gastrointestinal (Da Silva, Mauricio, Bering, & Correia, 2013; Mauricio, da Silva, Bering, & Correia, 2013; Ravasco, Monteiro-Grillo, & Camilo, 2012; Zhang, Lu, & Fang, 2014), head and neck (Chang et al., 2013), lung (Bagan et al., 2013), and kidney cancer (Ko et al., 2013). Neoplasia-related cachexia also has a worse outcome than non-oncological cachexia (Bachmann, Büchler, Friess, & Martignoni, 2013). However, the absence of a strict definition of cachexia, in particular when cancer-associated, obscures its real impact on morbidity and mortality (Wallengren, Lundholm, & Bosaeus, 2013). Fearon’s definition of cachexia, being at least 5% weight loss over the past 6 months, may offer an acceptable tool for evaluation of nutritional treatment.

The type of nutrients for resolving a cachectic state is debatable. One preclinical study found that adding fish oil reduced both cachexia and tumor growth in rats (Coelho et al., 2012). Such supplement also improved nutritional prognosis and plasma fatty acid profile in colorectal cancer patients (Mocellin et al., 2013). Conversely, vitamin D deficiency may increase the risk of developing breast cancer (Yousef et al., 2013). Anyhow, cancer cachexia most often results from anorexia which is a potentially treatable condition (Yennurajalingam et al., 2012). This is corroborated by our nutrition protocol which was based on biometric parameter-based dietary counseling and emanated in dietary recommendations that improved patient condition and outcome.

The patient’s well-being, measured as “quality of life,” is negatively affected by cachexia. Albeit still controversial, nutritional therapy is thought to ameliorate life quality (Uster et al., 2013). Also, improved prognosis in se might act as a possible confounder for evaluation of well-being. A multidisciplinary approach is recommended (Murphy & Girot, 2013). We did not measure quality of life because of the small patient sample size, yet our multidisciplinary approach proved to be effective.

Interestingly, no more weight loss was observed between 6 and 12 months of study in both groups. In fact, a patient (from either group) who deteriorated clinically and failed to take in sufficient feeding was allowed to receive enteral or even parenteral nutrition. This is standard practice in medical oncology healthcare, and it would be unethical to omit it for research purposes. Patients were not excluded from the study if this happened.

In conclusion, cancer-related cachexia can be effectively countered by a patient-tailored nutritional approach under supervision.

![Fig. 1. Unexpected hospitalization days from study enrollment up to 2 years after study ending. The linking symbol at the top of the graph demonstrates the statistical significance between the two groups. P = 0.0072.](image)

![Fig. 2. Kaplan–Meier curves showing patient survival from study enrollment up to 2 years after study ending. P = 0.0004.](image)
of a dedicated multidisciplinary nutrition team. This resulted in less longer duration of hospital stay and improved survival.

Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.appet.2015.04.049.

References


