Protocol Clinical Trial

Title of the project

Tight caloric control (TiCaCO) in the cachectic oncologic patient before the start of cancer therapy can stabilize body weight, thereby reducing morbidity and mortality: validation of the pilot trial. A randomized study.

Objective of the study

In our pilot trial, 20 patients were randomized, 10 receiving regular counseling by regular oncodietitians, while the 10 others received nutrition therapy. In the latter group, an assessment of biophysical parameters was made (including the bioelectrical impedance analysis or BIA for body composition), and their Energy Expenditure was assessed using indirect calorimetry. Afterwards, they received nutrition therapy according to the ESPEN (European Society for Parenteral and Enteral Nutrition) guidelines. Supplementary interventions were made to match caloric intake to energy expenditure (the 'Tight Caloric' approach), using enteral and parenteral nutrition if indicated, by an intensive coaching and follow-up to continue this nutrition strategy (with dieticians even being "on call" after hours). While the study follow-up lasted 2 years, nutrition therapy was only performed during the first 3 months. The results were striking: apart from keeping their body weight in balance, the patients of the nutrition therapy group counted much less unexpected hospitalisation days and they clearly lived much longer (De Waele, Appetite, 2015).

This project targets the validation of these results on a large scale. For this study, patients with either colorectal adenocarcinoma and non-small cell lung carcinoma, due to their high incidence as well as the high prevalence of cachexia in these patients will be included. While patients will be randomized, it is not possible to perform a double- or even single-blinded study due to the nature of the treatment. The recruitment phase will last 2 years, keeping refusals and dropouts in mind. Follow-up will last 2 years after inclusion, although the actual nutrition therapy will again last only 3 months: the period of active oncological treatment. An intermediate analysis is already made after the first year of follow-up. In case survival is already statistically significant, the trial will be stopped for ethical reasons. In case of a positive result, we want to implement nutrition therapy as a standard treatment in cachectic cancer patients in Belgium.

In case of a positive outcome (i.e. mere confirmation of our published results), the major advantage of nutrition therapy will be its relatively low cost while still affecting morbidity and mortality significantly. This can be practically achieved by redefining the dietician's task. The patient's own active participation in the decision making process is an important surplus in well-being and overall treatment. In combination with decreased morbidity and mortality the benefit of the patient can be found on every level.

Investigator(s)

PI and head of department of nutrition:
Elisabeth De Waele, MD, PhD: Elisabeth.DeWaele@uzbrussel.be
Intensive Care UZ Brussel

Co-investigator:
Joeri Pen, MD, PhD: Joeri.Pen@uzbrussel.be
Diabetes Clinic UZ Brussel

Sponsor *If applicable*
Baxter
Nutricia

Departments/laboratories involved in the study
Department of Nutrition: Elisabeth.DeWaele@uzbrussel.be
Department of Intensive Care:
Elisabeth.DeWaele@uzbrussel.be or Herbert.Spapen@uzbrussel.be
Department of Oncology: Jacques.DeGreve@uzbrussel.be

Introduction
Background

Cancer is a disease with a high prevalence and incidence worldwide, and often incurable because the diagnosis is made in an advanced stadium. Nevertheless, 50% of patients survive on average 10 years nowadays (accounting for all cancers together). This, however, does not necessarily equals a state of being cured from cancer. On the other end of the spectrum there are patients with a very poor prognosis from the beginning, regardless of treatment. The financial drawback is that the costs for treating cancer worldwide are the highest of any disease, accounting for nearly one trillion euro per year.

One major cause for a poor prognosis is the presence of malnutrition, due to a decreased intake, caused by the patient's symptoms. Symptoms can vary greatly, but are usually of gastrointestinal nature (nausea, vomiting), although general weakness and even depression can be present, all caused by advanced disease itself or by therapy (typically chemotherapy). Advanced disease is also marked by an increased resting energy expenditure, due to the tumor's induction of a hyperkatabolic state of the body. This will cause the clinical entity called "cachexia" and will eventually be responsible for the patient's demise. Although cachexia is usually referred to as a a body mass index (BMI) of < 20, in cancer a broader definition is used, whereby a weight loss > 5% over a period of 6 months is sufficient for the diagnosis, regardless of BMI (Fearon K, Nature Reviews Clinical Oncology, 2013).

This is the reason that restoration of the nutritional state of the patient, using nutrition therapy, is regarded as a promising form of supportive treatment of a cancer patient. It had already been shown that restoring the nutritional state will have a positive effect on wellbeing, morbidity, progression-free survival and possibly even overall survival (Rock CL, CA: a cancer journal for clinicians,2012). Finally, a recent pilot study was able to demonstrate higher overall survival using nutrition therapy, albeit the sample size was small (De Waele, Appetite, 2015).

One major advantage of nutrition therapy is its broad spectrum, being used both enterally and parenterally. Its potential is very large, as its advantages have been demonstrated for a wide array of cancers (depending on the study's setup). Moreover, nutrition can have a preventive role in the incidence of cancer. Nutrition therapy has even been shown to be effective in the

deadliest cancers, such as pancreatic cancer (Pericleous M, Anticancer research, 2014) and lung cancer (Koutsokera A, Clinical lung cancer, 2013). Despite of these results, the pathophysiology is only partly known (Suzuki H, J gastroenterology, 2013).

The strategy of nutrition therapy, however, may vary in the course of disease as both physiological as psychosocial changes can occur. It may easily be possible that a switch to tube feeding or even parenteral nutrition is needed, be it temporally or even permanently. This makes a holistic approach to nutrition mandatory, rather than focus on one or multiple food additives. In this regard, it has been shown that most supplements in monotherapy do not offer a single benefit (Ries A, palliative medicine, 2012).

This project targets the implementation of nutrion therapy in oncologic patients with cachexia, on a large scale. Its setup has been previously described in the domain of Intensive Care (Singer P, Intensive Care Medicine, 2011), and has proven to be fruitful in our pilot study (De Waele, Appetite, 2015).

Rationale

In our pilot trial, 20 patients were randomized, 10 receiving regular counseling by regular oncodietitians, while the 10 others received nutrition therapy. In the latter group, an assessment of biophysical parameters was made (including the bioelectrical impedance analysis or BIA for body composition), and their caloric status was assessed using indirect calorimetry. Afterwards, they received nutrition therapy according to the ESPEN (European Society for Parenteral and Enteral Nutrition) guidelines and supplementary matching caloric intake to energy expenditure (the 'Tight Caloric' approach) by an intensive coaching and follow-up to continue this nutrition strategy (with dieticians even being "on call" after hours). While the study follow-up lasted 2 years, nutrition therapy was only performed during the first 3 months. The results were striking: apart from keeping their body weight in balance, the patients of the nutrition therapy group counted much less unexpected hospitalisation days and they clearly lived much longer (De Waele, Appetite, 2015).

This project targets the validation of these results on a large scale. For this study, patients with either colorectal adenocarcinoma and non-small cell lung carcinoma, due to their high incidence as well as the high prevalence of cachexia in these patients. While patients will be randomized, it is not possible to perform a double- or even single-blinded due to the nature of the treatment. The recruitment phase will last 2 years, keeping refusals and dropouts in mind. Follow-up will last 2 years after inclusion, although the actual nutrition therapy will again last only 3 months. An intermediate analysis is already made after the first year of follow-up. In case survival is already statistically significant, the trial will be stopped for ethical reasons. In case of a positive results, we want to implement nutrition therapy as a standard treatment in cachectic cancer patients in Belgium.

In case of a positive outcome (i.e. mere confirmation of our published results), the major advantage of nutrition therapy will be its relatively low cost while still affecting morbidity and mortality significantly. This can be practically achieved by redefining the dietician's task. The patient's own active participation in the decision making process is an important surplus in well-being and overall treatment. In combination with decreased morbidity and mortality the benefit of the patient can be found on every level.

Study design
randomized controlled double-blind parallel-group multi-centre study

Medication/device *If applicable*

Not applicable (enteral and parenteral nutrition, commercially available)

The subjects

Number of subjects

- Colorectal cancer (CRC) st. III - IV (TNM system) with cachexia
- Non-small cell lung cancer (NSCLC) st. III - IV (TNM system) with cachexia

120 subjects in each group, 60 controls and 60 Nutrition Therapy patients, based on statistical power. 20% extra patients were added to this number to account for dropouts.

Investigational group (Group A)

At the time of diagnosis, patients will immediately be screened and started with Nutrition Therapy if assigned to group A. This regimen will stay in place for 3 months, after which a switch will be made towards normal dietary counselling. Nutrition Therapy can be given orally, parenterally or via tube feeding, depending on the patient's status and aims at matching caloric Intake with Resting Energy Expenditure. Moreover, a switch between these modalities is possible during these 3 months. Afterwards, standard dietary counselling will be given during the remainder of the study. Follow-up will last 1 year. If one year after the last enrolment the study shows a large difference with the control group, the study will be stopped for ethical reasons.

Reference group (Group B)

At the time of diagnosis, patients will immediately be screened and started with standard dietary counselling for 2 years if assigned to group B. Dietary intervention can be orally, parenterally or via tube feeding, depending on the patient's status. Moreover, a switch between these modalities is possible during these 3 months. Follow-up will last 1 year. If one year after the last enrolment the study shows a large difference with the control group, the study will be stopped for ethical reasons.

Both Groups:

Oncological treatment will be performed at the discretion of the participating specialists, following the ESMO guidelines. Although an open label study, the oncologic treatment will not be related to the dietary regimens.

Inclusion is to take place in a period of one year. The duration of the study for each subject from randomisation to end of treatment is three months and a follow up period of nine months, for a total of one year per patient. Afterwards, analysis will take place.

Power calculation:

96 patients per cancer group (48 controls and 48 nutrition therapy), supplemented with 20% per group to take dropouts into account.

Inclusion criteria

- > 18 years
- Male and female
- CRC or NSCLC before chemo- or radiotherapy is started (naive to treatment), but surgery may already have been performed
- CRC or NSCLC relapse > 3 months after initial oncologic therapy
- Oncologic cachexia (undesired weight loss > 5% in less than 6 months)
- Written informed consent / ability to give informed consent

Exclusion criteria

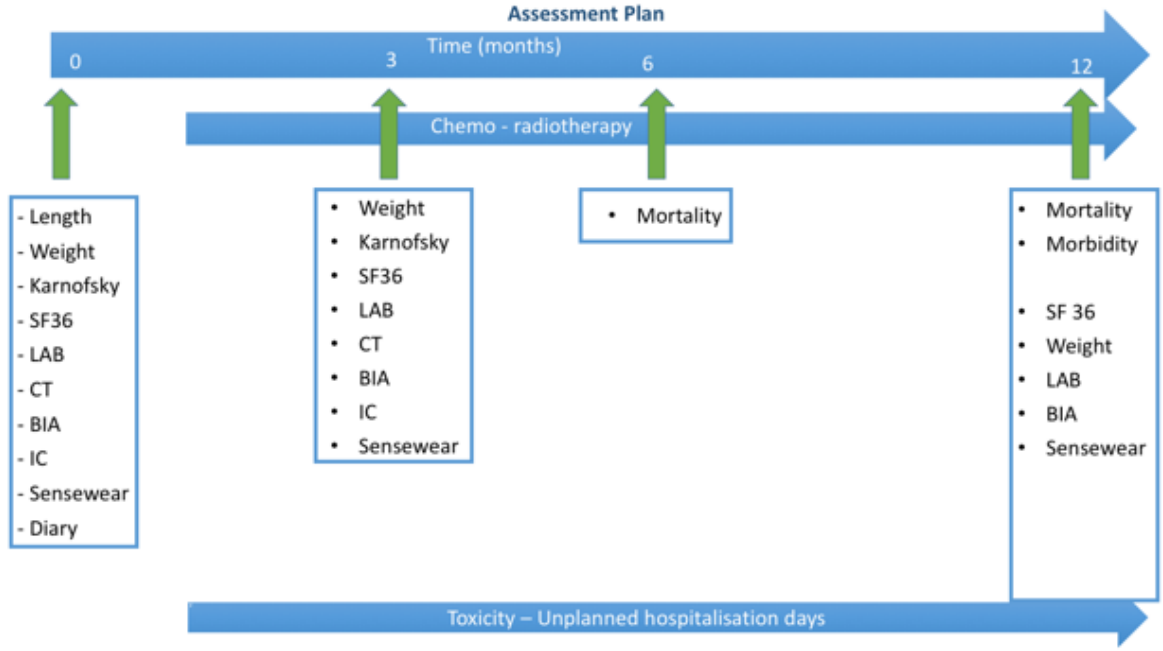
- concomitant second malignancy
- uncertainty of diagnosis of CRC or NSCLC
- patient unfit for chemotherapy
- patient unfit for radiotherapy
- patient unfit for surgery
- palliative treatment or terminal patient (life expectancy < 3 months)
- patient already participating in another study
- Pregnancy / lactation
- Any other pathology present that causes the patient to be unfit for oncologic therapy (e.g. end-stage renal failure, severe COLD, severe heart failure)
- Unable to adhere to protocol instructions (e.g. language barrier)
- Investigator's uncertainty about the willingness or ability of the patient to comply with the protocol requirements
- Participation in any other studies involving investigational or marketed products concomitantly or within two weeks prior to entry into the study

Replacement of subjects
In case of dropout, subjects will be censored on the Kaplan-Meier curves.

Restrictions and prohibitions for the subjects
None.

<u>Procedures</u>
See below, to be performed at the oncology consultation.

Flowchart



systematic overview of the study: planned tests per visit of the subjects

Expected total duration of the trial: 2 year (inclusion).
Supervising MD during the tests: Principal Investigator: Dr. De Waele or co-investigator: Dr. Pen.

Randomisation/blinding

Computerized randomization, validated for clinical trials, are used.

Prior and concomitant therapy

See "Inclusion and Exclusion criteria". All other concomitant therapy is allowed.

Study analysis

Sample size calculation

The statistical power was calculated based on the pilot trial.

Analysis of the samples

Outcome parameters:

• Body weight
• BIA Bio-Electrical Impedance Analysis
• Blood Pressure
• Blood Sample Analysis
• Caloric and Nitrogen intake
• Indirect Calorimetry
• Sensewear ®
• Body weight
• BIA Bio-Electrical Impedance Analysis
• Blood Pressure
• Blood Sample Analysis
• Indirect Calorimetry
• Body weight, mortality, morbidity.

- Primary: weight stabilisation, morbidity and mortality
- Secondary: Quality of Life (QoL 36)

Statistical analysis
2-tailed, paired t-tests will be used for statistical analysis.

Quality control and quality assurance

The quality control is performed by the certified and experienced research unit of the Intensive Care Department.

Publication policy

All rights belong to the PI and thus to the VUB/the UZ Brussel.

Protocol Amendment dd 12/06/2017

Background:
Due to lack of patients with 5% weight loss in 6 months and, by consequence, very low inclusion rate, it was decided to amend the protocol. To achieve this, a special cooperation with the department of Radiotherapy was established. The service sees many patients who lose weight during radiotherapy, partly because of cancer-related cachexia, but mostly due to the mucositis caused by radiotherapy itself, losing > 10% of their initial body weight (at the start of their therapy). This is especially seen in cancers of head and neck, oesophagus and stomach. Radiotherapy is performed on working days and treatments typically last 5-7 weeks (depending on indication).

Amendment:

- Inclusion of patients with colorectal, lung and pancreatic cancer will be changed to: Inclusion of patients with lung, gastric, oesophageal, head and neck and pancreatic cancer
- 5% weight loss over the past 6 months will be changed to: patients with the aforementioned cancers where radiotherapy will be part of their treatment (or will be the entire treatment)
- Duration of intervention of 3 months will be changed to: duration of intervention for the entire period of radiotherapy
- After recalculation of statistical power, only 48 patients will be needed instead of 96. With correction for dropouts, this will become 60 patients instead of 120. This means 30 controls and 30 patients in the intervention group.
- The amendment will be added to the registration at *clinicaltrials.gov*.

The procedure and flowchart will remain unchanged. Analysis of the data will remain: in whole, per cancer and per sex (the latter two criteria requiring 60 patients in each group).

<u>Protocol Amendment dd 19/09/2017</u>

Background:

The study has seen much more inclusions and is running well thanks to the previous amendment. Due to a typo, the colorectal cancer group was unfortunately omitted. Also, the absolute difference of survival in the TiCaCo trial after one year was similar to that after the second year.

Amendment:

- Colorectal cancer patients are still to be included. Otherwise, nothing changes concerning inclusion criteria.
- The follow-up will be shortened from 2 years to one year.
- The amendment will be added to the registration at *clinicaltrials.gov*.

<u>Protocol Amendment dd 05/02/2019</u>

Background:

The study needs 48 inclusions that remain in the study until the end. However, the number of dropouts is too high, severely compromising the study's statistical power. Therefore, an inclusion surplus of 20 - 25% is required.

Amendment:

- The inclusion period will be expanded to 31/12/2019 or the inclusion of 60 patients (including dropouts), whichever is sooner.
- The amendment will be added to the registration at *clinicaltrials.gov*.