GATAC: Asian ginseng (Panax Ginseng) for the treatment of Cancer-Related Fatigue: a randomized, double-blind controlled study.

Background

Cancer-related fatigue (CRF) is the most common symptom in patients with cancer. Fatigue appears before the cancer is diagnosed, typically increases during chemo-radiotherapy and remains after the treatment.
The NCCN (National Comprehensive Cancer Network) defines CRF as "an unusual, persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning".
CRF prevalence is about 60-90%, related to clinical setting and has a significant impact on patients quality of life and ability to carry out normal daily activities.
The etiology of CRF is multifactorial, as extent of disease, cancer treatments, depression, malnutrition, anemia, insomnia, are the most frequent causes.
Actually, there is no pharmacologic treatment specifically indicated to CRF. With the exception fatigue due to anemia, for which the treatment with erythropoietin has been demonstrated a positive effect, there is no scientific evidence for corticosteroids, antidepressant and L-carnitine.
Since CRF is a subjective sense, the quantification is not univocal. A lot of scales were proposed, unidimensional and multidimensional, that vary for the number of variables evaluated and the quantification of fatigue. The unidimensional scales evaluate only the physical aspects of fatigue, while multidimensional scales evaluates also the quality of life. An example of unidimensional scale is the Brief Fatigue Inventory (BFI), while an example of multidimensional scale is the EQ5D.
Ginseng or Panax is a gender of 11 species that belongs to the Araliaceae family. The two species that have been most extensively researched and studied are Panax ginseng (Asian) and Panax quinquefolius (American).
Ginseng is often referred as "adaptogen", that suggest that it has various effects, such as anti-fatigue and anti-stress agent. These activity are due to ginsenosides. Recently, in United States, two pilot studies reported the positive effects of American ginseng on CRF.

Objectives

The primary objective of this study is the improvement of CRF, evaluated as the reduction of the score at the BFI scale.
Secondary objectives are the improvement of the quality of life, evaluated with the EQ5D scale, and the definition of the safety profile of Asiatic ginseng, evaluated with Common Terminology Criteria for adverse events (version 3.0).
Primary endpoint is the grade of fatigue evaluated with the BFI scale.

Study design

This is a multicentric, controlled, randomized, double-blind study which compare two doses of ginseng to placebo.
Investigators of the Centres involved in the project will select patients and, after obtaining Informed Consent will randomize them in one of the three treatment arms. The patient will receive a diary and the treatment for eight weeks.

Inclusion Criteria

- Patient with a median fatigue score ≥ 4 with BFI
- Patient who belong to one of the following groups:
  1) patients who finished an adjuvant chemotherapy for breast cancer, or colo-rectal cancer or ovarian cancer or lung cancer and with no evidence of disease
  2) patients with metastatic cancer, progressive after a first line that must begin a second or third line
  3) patients with progressive advanced cancer, no more eligible for chemotherapy
- Patient with life expectancy > 6 month
- Patient with Performance Status 0-1
- Patient who have signed Informed Consent
- Patient older than 18 years old

Exclusion Criteria

- Patient with anemia (hb < 9g) or hypothyroidism uncompensated with therapy or with persistent insomnia
- Patient with diabetes in treatment with oral hypoglycaemic and/or insulin
- Patient in treatment with Warfarin and with history of bleeding
- Patient who begun an anxiolytic therapy from less that 2 month or anxiolytic therapy with a unstabilized dosage
- Patient who will undergo radiotherapy or surgical procedures
- Patient who already use commercial products with ginseng
- Patient who inconstant use supplements
- Patient with arterial hypertension not controlled by drugs
- Patient with history of acute asthma
- Patient who are not able to swallow capsules
- Pregnant or breast-feeding woman
- Fertile woman who refuse appropriate contraceptive

Treatment

Patient will be randomized into three treatment arms:
A) ginseng 250 mg/die,
B) ginseng 500 mg/die,
C) placebo.
The treatment will consist of two daily oral intake of one capsules of ginseng / placebo at 08:00 and at 13:00. Group A will receive 1 capsule of ginseng and one of placebo, group B will receive 2 capsules of ginseng and group 3 will receive 2 capsules of placebo. Treatment will last 8 weeks.

Experimental material

The Pharmaceutics Laboratory of the Hospital Pharmacy of the Policlinic S.Orsola-Malpighi of Bologna will prepare capsules containing 250 mg of ginseng/placebo for all the centres involved to the trial. The Pharmacy and the Coordinating centre will also send the supplements/placebo to the centres.

Toxicity
Panax ginseng is usually well tolerated and related side effects are usually mild and reversible with the treatment discontinuation.
Non serious side effects related to ginseng includes: nausea, diarrhea, euphoria, insomnia, headache, hypertension, hypotension, mastalgia and vaginal bleeding.
Ginseng interact with caffeine and increase arterial blood pressure.

Dose reductions and discontinuation
There will not be dose reduction during the study.
In case of unacceptable toxicity, the treatment will be discontinued.
After discontinuation, patient will be followed for 30 day to check new adverse events.

Size of the study
Based on the results of the pilot study by Barton et al. to the Mayo Clinic in which the American ginseng induced a benefit on fatigue in 40% of patients treated with two higher doses compared with 17% of patients treated with placebo, we believe that in the present study results to be reached is to obtain a benefit on CRF, measured by the scale BFI, in 40% of cases treated with ginseng and in 15% of patients treated with placebo. To reach the significance of this difference with a power of 80% and an alpha error of 5% the number of patients to be enrolled per arm is 69, it follows that for each of the 3 cohorts, the number will be 207 and that the overall study should provide a total of 621 patients.