DIetary REstriction as an adjunct to neoadjuvant ChemoTherapy for HER2 negative breast cancer

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PrimaryDoes a peri-chemotherapeutic FMD ameliorate grade III or IV toxicity (Phase II part) and increase pathologic complete response (pCR) in patients with HER2 negative early breast cancer treated with neoadjuvant chemotherapy (Phase III part)....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON44768

Source
ToetsingOnline

Brief title
DIRECTstudy

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, mamma carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: BOOG Study Center
Source(s) of monetary or material Support: Pink Ribbon

Intervention

Keyword: breast cancer, fasting mimicking diet, neoadjuvant chemotherapy, pathological complete response

Outcome measures

Primary outcome

* The percentage of patients with grade III/IV toxicity to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (phase II).

* The percentage of pathological complete response according Miller and Payne (phase III).

Secondary outcome

Secondary endpoints:

* To determine the effect of FMD on the clinical response measured by MRI (RECIST1.1) halfway therapy.

* To determine the effect of FMD on grade I/II side effects of chemotherapy according to NCI CTCAE v4.03.

* Metabolic (Glucose, insulin, insulin-like growth factor-I (IGF-I), insulin-like growth factor binding protein 3 (IGF-BP3), free thyroxin (FT4), T3 and thyroid-stimulating hormone (TSH)) and inflammatory response (CRP) to chemotherapy.

* DNA damage, apoptosis, immunology and nutrient sensing system activity in the tumor.

* Patient*s quality of life (using EORTC QLQ-C30 and EORTC QLQ-BR23

questionnaires), burden of therapy noted by a visual analogue scale (VAS)

(Distress Thermometer) and differences of Illness Perceptions (B-IPQ).

* Long term efficacy of treatment (DFS, OS).

* Hormone receptor percentage, Ki67 and immunologic tumor profile and

tumor/stroma ratio as predictive biomarker.

* SNPs used as biomarker to predict treatment outcome.

Side study endpoints:

* Protein profiles and cytokines used as biomarker to predict treatment outcome

* Quantification of chemotherapy-induced DNA damage in leukocytes (with *-H2AX

modification and comet assay).

* Quantification of nutrient sensing system gene expression (with western

blot).

Study description

Background summary

Evidence from experimental animals provides strong support for the concept that fasting evokes resistance to multiple forms of stress. Fasting reduces plasma levels of growth factors (e.g. insulin-like growth factor-I) and modulates intracellular nutrient sensing systems, thereby diverting energy from growth to maintenance. Accordingly, the currently available preclinical evidence suggests that short-term fasting protects normal cells against the perils of (high dose) chemotherapy. In contrast, cancer cells are not (or less) protected, as a result of their self-sufficiency in growth signals. This phenomenon is termed Differential Stress Resistance (DSR). DSR reduces the severity of toxic side-effects of chemotherapy and interestingly, it simultaneously renders cancer cells more vulnerable to chemotherapeutics. A recent report of a case series of 10 cancer patients suggests that short term fasting protects against

the side effects of chemotherapy in humans. Indeed, the majority of patients preferred fasting to feeding in preparation of their therapy.
Obviously, fasting is not an easy thing to do for most of us. Importantly, extensive preclinical evidence and preliminary clinical data indicate that a specifically designed very low calorie, low amino acid substitution diet (*Fasting Mimicking Diet, FMD*) has effects on cancer therapy that are very similar to those of fasting. This study aims to further evaluate the impact of the FMD on tolerance to and efficacy of neo-adjuvant chemotherapy in women with stage II or III breast cancer.

Study objective

Primary
Does a peri-chemotherapeutic FMD ameliorate grade III or IV toxicity (Phase II part) and increase pathologic complete response (pCR) in patients with HER2 negative early breast cancer treated with neoadjuvant chemotherapy (Phase III part).

Secondary
* Does a peri-chemotherapeutic FMD reduce
* grade I/II side effects of chemotherapy
* the metabolic and inflammatory response to chemotherapy.
* Does a peri-chemotherapeutic FMD increase
* Clinical response
* DNA damage, apoptosis, immunology and nutrient sensing pathways in the tumor.
* the patient*s quality of life.
* long term efficacy of treatment (disease-free survival (DFS) and overall survival (OS)).
* Study predictive biomarkers (hormone receptor percentage, Ki67, immunologic tumor profile and tumor/stroma ratio) of the tumor.
* Determine single nucleotide polymorphisms (SNPs) that can be used as biomarker to predict treatment outcome in these patients using a FMD.

Side studies
* Determine protein profiles (proteomics) and cytokines that can be used as biomarker to predict treatment outcome in these patients using a FMD.
* Does a peri-chemotherapeutic FMD reduce chemotherapy-induced DNA damage in leukocytes.
* Does a peri-chemotherapeutic FMD increase activation of energy sensing pathways in leukocytes.

Study design

Prospective, open, multicenter, randomized phase II/III intervention study

Intervention

Chemolieve* for 3 days prior to and the day of chemotherapy and 3 days prior to surgery versus regular diet.

Study burden and risks

There are potential risks and discomforts associated with low calorie and low protein diets like Chemolieve*, such as hunger, drowsiness, dizziness, headache, muscle aches, fatigue and low blood pressure. Bodyweight will be monitored in the course of the trial to detect *10% weight loss, which will be a reason for withdrawal from further participation. The benefits obviously remain to be established, but they are potentially substantial.
There is a possibility that patients experience more nausea because of leaving out dexamethasone as an anti-emetic in the intervention group during the AC or FEC cycles. To reduce this risk, patients will receive metoclopramide instead and if they experience serious nausea, dexamethasone will be given the next cycles.

Contacts

Public
BOOG Study Center

Plesmanlaan 125
Amsterdam 1066 CX
NL
Scientific
BOOG Study Center

Plesmanlaan 125
Amsterdam 1066 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Female patients with stage II or III breast cancer receiving neoadjuvant 4AC>4T or 3FEC>3T
* Measurable disease (breast and/or lymph nodes)
* HER2 negative core biopsy
* Age *18 years
* WHO performance status 0-2
* Adequate bone marrow function : white blood cells (WBCs) *3.0 x 109/l, neutrophils *1.5 x 10^9/l, platelets *100 x 10^9/l
* Adequate liver function: bilirubin *1.5 x upper limit of normal (UNL) range, ALAT and/or ASAT
*2.5 x UNL, Alkaline Phosphatase *5 x UNL
* Adequate renal function: the calculated creatinine clearance should be *50 mL/min
* Patients must be accessible for treatment and follow-up
* Written informed consent according to the local Ethics Committee requirements
* Willing to fill in quality of life questionnaires
* Able to read and write in Dutch

Exclusion criteria

* History of invasive breast cancer or ipsilateral non-invasive breast cancer
* Previous malignancy within 5 years, with exception of a history of a previous basal cell carcinoma
of the skin or pre-invasive carcinoma of the cervix.
* Serious other diseases such as recent myocardial infarction, clinical signs of cardiac failure or
clinically significant arrhythmias
* Diabetes Mellitus
* Body mass index (BMI) < 19 kg/m2
* Pregnancy or lactating
* Significant food allergies which would make the subject unable to consume the food provided (ex:
nuts or soy)
* Any metabolic disorders that may affect gluconeogenesis or adaptation to short fasting periods.
* Medical or psychological condition which in the opinion of the investigator would not permit

the
patient to complete the study or sign meaningful informed consent

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-03-2014
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO Date:	12-09-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-12-2013
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-02-2014

Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	12-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	03-12-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-03-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-12-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	14-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	26-04-2017
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL44684.058.13