DIRECT-2: Fasting mimicking Diet Program to ImpRovE ChemoTherapy in HR+, HER2- breast cancer

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To improve the pathological response rate according to Miller and PayneTo improve quality of life including cognitionTo determine the effect of FMD on local tumor immunity

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

Summary

ID

NL-OMON51480

Source
ToetsingOnline

Brief title
DIRECT-2

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mamma carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: KWF (Koningin Wilhelmina Fonds) WCRF (World Cancer Research Fund),L-Nutra

Intervention

Keyword: Breast Cancer, Fasting mimicking diet (FMD), Neoadjuvant Chemotherapy, Short-term fasting (STF)

Outcome measures

Primary outcome

- Pathologic response-rate (increase in 90-100% tumor-cell loss) and/or pathological complete response (pCR) scored on the surgical tumor resection material.

- objective response rate (ORR) assessed by MRI according to Response Evaluation Criteria In Solid Tumors (RECIST)1.1 criteria performed at baseline, after 4 ddAC cycles and at the end of chemotherapy.

Secondary outcome

- 3 and 5 year Event free survival (EFS) and overall survival (OS)

- Adverse events >=grade 3 (maximum total) difference between treatment arms during ddAC, T and total duration of neoadjuvant chemotherapy.

- QoL assessed using validated online questionnaires at T0, T1, T2 and T3.

- Cognition assessed by the Amsterdam Cognition Scan (ACS) at T0, T2 and T3. This is a validated online cognitive test battery that can be completed at home.

- Local immunomodulation and tumor immunity by analyzing the immune-composition and gene-expression profile using exploratory immune analyses, including multispectral imaging (e.g. Vectra) and transcriptomics using Nanostring in tumor samples taken at baseline (diagnostic), after 4 cycles and resection specimen.

Study description

Background summary

In preclinical research, short-term fasting (STF) protects tumor-bearing mice against the toxic effects of chemotherapy, improves the CD8+ effector T-cell intratumor infiltration, while enhancing the chemotherapy efficacy. Short-term use of a "fasting-mimicking diet" (FMD) caused a major increase in the efficacy of cancer treatment in mice comparable to STF. In humans, we recently performed a multicenter randomized phase II trial showing that patients with Human Epidermal growth factor Receptor 2 (HER2) negative breast cancer treated with neoadjuvant chemotherapy and FMD displayed a better radiological response and a better pathological response (90-100% vs <90% tumor cell reduction) than patients treated with chemotherapy without FMD. Therefore the goal is validate the effect of an FMD during neoadjuvant chemotherapy in a phase 3 trial. That is why we hypothesize that FMD during neoadjuvant chemotherapy for hormone receptor positive, HER2 negative breast cancer improves pathological response rate and quality of life including cognition, potentially due to improved local immunity.

Study objective

To improve the pathological response rate according to Miller and Payne
To improve quality of life including cognition
To determine the effect of FMD on local tumor immunity

Study design

DIRECT-2 will be a multicenter, randomized, open label, phase III trial coordinated by the Dutch Breast Cancer Research Group (BOOG) for patients with hormone receptor positive and HER2-negative breast cancer with an indication for neoadjuvant chemotherapy consisting of 2-weekly dose dense adriamycine and cyclophosphamide (ddAC) for 4 cycles followed by 12 times weekly paclitaxel (T). Participants will be randomized to receive an FMD 3 days prior to and the day of chemotherapy administration, every 4 weeks during chemotherapy (2x during ddAC and 3x during T) or their regular diet. Histopathological response will be assessed on the surgical tumor specimen. Additionally, an extra tumor biopsy will be obtained after 4 ddAC cycles for investigation of tumor-immunity modulation. Clinical response will be evaluated by MRI after 4 cycles ddAC and at the end of chemotherapy. Quality of Life will be measured at baseline, 1-2 weeks after the last ddAC, 2-3 weeks after the end of chemotherapy and 6 months after surgery. Cognition will be determined at baseline, 2-3 weeks after the end of chemotherapy and 6 months after surgery.

Intervention

Fasting mimicking diet by L-Nutra, a 4-day low caloric, low protein, vegetarian diet 3 days prior to and the day of neoadjuvant chemotherapy administration. The FMD will take place every 4 weeks, thus in total 5 times (2x during ddAC, 3x during Paclitaxel) during the neoadjuvant chemotherapy. The control arm will follow regular diet.

Study burden and risks

Participating patients have to be willing to follow the 4-day FMD diet every 4 weeks during chemotherapy (5 times in total) and extra blood sampling during routine. A relative risk for participating patients regarding the 4-day FMD includes mild side-effects such as: feelings of hunger, headache, nausea, lack of energy. After 4 ddAC cycles, an additional tumor biopsy will be obtained. There is also extra burden for the online quality of life and cognition questionnaires up until six months after surgery. Ample experience with a much more extensive test battery for cognition in many patient populations has indicated that such a procedure is feasible. The neuropsychological examination (online test battery) to assess cognition does not pose any risk for patients, albeit it takes around 50 minutes to complete.

Contacts

Public
Leids Universitair Medisch Centrum

Albinusdreef 2
LEIDEN 2333 ZA
NL
Scientific
Leids Universitair Medisch Centrum

Albinusdreef 2
LEIDEN 2333 ZA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Clinical stage II-III, hormone receptor positive, HER2 negative breast cancer
• Detectable and measurable disease (breast and/or lymph nodes)
• Age >=18 years old
• WHO performance status 0-2
• Ability to read and understand Dutch language, accessibility to a computer with internet connection and independent use of computer

Exclusion criteria

• Patient history of invasive breast cancer or ipsilateral non-invasive breast cancer
• Active malignancy in the last 5 years, with the exclusion of basal cell carcinoma or pre-invasive cervical neoplasia/dysplasia.
• Body mass index (BMI) < 18.5 kg/m2
• Pregnancy or lactating
• Food allergy for ingredients of FMD (nuts, soy, honey)
• A metabolic condition affecting gluconeogenesis or adaptation to periodic fasting. (Diabetes Mellitus for example)

Study design

Design

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

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-04-2023
Enrollment:	240
Type:	Actual

Ethics review

Approved WMO

Date:	05-01-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL80749.058.22