Phase III randomized trial with neoadjuvant chemotherapy (TAC) with or without zoledronic acid for patients with large resectable or locally advanced HER2-negative breast cancer.

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

Summary

ID

NL-OMON34755

Source
ToetsingOnline

Brief title
NEO-ZOTAC

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: BOOG Study Center B.V
Source(s) of monetary or material Support: Deze investigator initiated studie wordt gefinancierd door het BOOG Study Center;uitvoeringsorgaan van de Borstkanker Onderzoek Groep (BOOG). De BOOG krijgt haar fondsen deels uit subsidies van KWF en de industrie. Daarnaast wordt de deelnemende ziekenhuizen gevraagd om eventuele extra kosten als METC kosten voor hun rekening te nemen.

Intervention

Keyword: Breast cancer, Neoadjuvant chemotherapy, Pathologic complete response, Zoledronic acid

Outcome measures

Primary outcome

The primary objective of this study is to determine the pathologic complete

response (pCR) rate to neoadjuvant chemotherapy with or without zoledronic acid

at surgery.

Secondary outcome

-Clinical response (partial and complete according to RECIST v 1.1) of

neoadjuvant therapy correlated to pathological response.

- Disease free survival and overall survival after 3 and 5 years correlated to

pCR

-Tolerability (grade 3 / 4 CTC toxicities) of both regimens.

-Pathology: ER/PR and HER2 heterogeneity in core biopsy vs. operation specimen.

Study description

Background summary

Neoadjuvant chemotherapy is an effective alternative to adjuvant chemotherapy in both early and locally advanced breast cancer. Neoadjuvant chemotherapy has

the advantage that it potentially downstages the tumor, facilitating breast conserving surgery instead of a mastectomy. Additionally it provides information of response of the tumor to treatment and it allows research of pathological and molecular predictors of response and tumor biology. In the neoadjuvant setting the regimen using six cycles of docetaxel, adriamycin and cyclofosfamide (TAC) is generally accepted as standard care.
It has been recently discovered that bisphosphonates (BPs), especially the most potent BP zoledronic acid, might have both anti tumor effects and a synergistic effect when given sequential with chemotherapy. Clinically, after previous discordant data using less potent bisphosphonates in the adjuvant setting the ABCSG-12 trial was the first adjuvant clinical trial to notice an improvement of disease-free survival, a reduction in distant metastasis other than bone, loco-regional and contra lateral relapses and a trend to reduces risk of death, with zoledronic acid (4mg every 6 months for 3years) added to endocrine treatment.
In a large trial (AZURE) investigating the anti tumor effects of zoledronic acid in the neoadjuvant and adjuvant treatment of breast cancer, an interim analysis of the subset treated with neoadjuvant chemotherapy showed an significant improvement in pathological complete response (10,9 % vs. 5,8%) when zoledronic acid was added.The mechanism of this synergy is currently unknown.

Study objective

In this study we want to investigate whether the submission of zoledronic acid to neoadjuvant chemotherapy benefits the pathological complete response, and thus favors a better clinical outcome in patients with large ressectable or locally advanced HER2-negative breast cancer.
Further we want to evaluate the clinical response, DFS and OS in correlation with the pathological response. We also evaluate the toxicity of both treatment arms en the heterogeneity of the core biopsy and operation specimen.
By means of translational research, we try to investigate the mechanism of action of zoledronic acid en try to detect methods for early respons detection in neoadjuvant treatment.

Study design

This study is designed as a randomized, open-label, multi centre phase III trial.

Intervention

Arm A: Zoledronic acid 4 mg i.v in 15 minutes every 3-weeks within 24 hours after infusion of chemotherapy, repeated every 21 days for 6 cycles

Study burden and risks

Patients are randomised in group A (TAC with zoledronic acid) or group B (TAC). Patients in group A will receive 4 mg of zometa in 15 minutes, within 24 hours after infusion of all chemotherapeutic agents. No extra visits or investigations are planned unless patients particpate in one or more of the side studies.
The most common treatment-related adverse event is an acute phase reaction, a transient flu-like syndrome of fever, arthralgias and myalgias starting within 24 hours after treatment. Paracetamol can be used to prevent this flu-like syndrome.Zoledronic acid dosis > 4 mg, especially when infused over < 15 minutes, were associated with a greater risk of serum creatinine increase. Rarely, osteonecrosis of the jaw is seen especially in combination with dental surgery and is associated with high cumulative dosage en longer treatment periods. In case of poor dental health, patients should visit their dentist before starting the neoadjuvant therapy. Dental surgery during neoadjuvant treatment with zoledronic acid is strongly advised against.
If our hypothesis that adding zoledronic acid to neoadjuvant chemotherapy improves pCR is correct, patients could benefit because a pCR is related with a better clinical survival and an increased disease free survivall. Patients could also benefit by being able to receive a breast conserving operation instead of a mastectomy if the tumor shrinks more when treatment is in combination with Zometa.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Women presenting with large resectable or locally advanced breast cancer (T2 >=2 cm and positive lymph nodes, T2 >= 3cm* T3,T4, every N, M0)
•Measurable disease (breast and/or lymph nodes)
•Histological proven HER2-negative breast cancer in the core biopsy material.
•Age >=18 years
•WHO 0-2
•Adequate bone marrow function (within 14 days prior to registration): WBC >=3.0 x 109/l, neutrophils >=1.5 x 109/l, platelets >=100 x 109/l
•Adequate liver function (within 4 weeks prior to start treatment): 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

Exclusion criteria

•Evidence of distant metastases (M1)
•Prior surgery other than biopsy
•Prior chemotherapy or radiation therapy
•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.
•Prior bisphosphonate usage.
•Peripheral neuropathy > grade 2, whatever the cause
•Serious other diseases as recent myocardial infarction, clinical signs of cardiac failure or clinically significant arrhythmias.
•Poor dental health.
•Known hypersensitivity reaction to any of the components of the treatment
•Pregnancy or lactating

Study design

Design

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

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-07-2010
Enrollment:	250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cyclophosphamide
Generic name:	Endoxan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Neulasta
Generic name:	Pegfilgrastim
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zometa

Generic name:	Zoledronic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-01-2010
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-03-2010
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
EudraCT	EUCTR2009-016932-11-NL
CCMO	NL30600.058.09