A randomized, prospective trial of 3 weeks pre-operative hormonal treatment for hormone receptor positive breast cancer: Anastrozole, Fulvestrant or Tamoxifen Exposure - Response in molecular profile (AFTER).

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

Summary

ID

NL-OMON41277

Source
ToetsingOnline

Brief title
AFTER study; pre-operative hormonal treatment

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mammary neoplasms

Research involving

Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Astra Zeneca,AstraZeneca

Intervention

Keyword: breast cancer, drug resistance, endocrine treatment, pre-operative treatment

Outcome measures

Primary outcome

Change in tumor cell proliferation. Proliferation will be measured by (change in) Ki67 expression and Cyclin A, apoptosis by the TUNEL assay. We will try to correlate the "TAMRO-profile", the phospho-PKA expression, and the phosphorylation extent of Serine305 with these parameters.

Secondary outcome

- Investigate different gene-profiles with proven predictive value for endocrine resistance

• Compare the changes in gene expression in the different study arms with changes in proliferation index

• To collect blood samples of all patients for research on SNPs in CYP450 sequences in normal and tumor DNA.

• To collect tumor material for research on downregulation of ER and PgR.

• To collect blood samples to evaluate whether (a change in) estrogen serum levels correlate with outcome.

• To study the relationship among concentrations of tamoxifenmetabolites in serum and tumormaterial and expression levels of CYP450 sequences in the tumor.

- Investigate paired tumor samples by ChIP-sequencing for response-predicting

changes in estrogen-receptor binding sites

- To collect blood samples to evaluate the effect of endocrine therapy on the

immune system.

Study description

Background summary

It is unclear how the recently validated, predictive gene expression profile for tamoxifen resistance in metastatic breast cancer (*TAMRO profile*) performs in the pre-operative or adjuvant setting. Nor is it clear whether this profile predicts endocrine therapy resistance in general, or is specific for tamoxifen treatment. In addition, we hypothetize that after short-term exposure of breast cancer patients to endocrine treatment a change in the molecular profile of the tumor will take place. This change could be predictive for endocrine therapy resistance.
Recently it has been shown PKA-mediated phosphorylation of Ser305 confers resistance to tamoxifen in vitro. Our group revealed a correlation between highly expressed phospho-PKA in combination with a high extent of Ser305 phosphorylation and worse outcome after first line palliative tamoxifen for metastatic disease. We will try to validate these findings prospectively.

Study objective

To investigate prospectively how the "TAMRO-profile" performs in a pre-operative treatment setting. In addition we can examine whether the profile is specific for tamoxifen or is predictive for endocrine resistance in general. Also the correlation between phospho-PKA in combination with phospho-Serine305 and tamoxifen resistance can be confirmed in a prospective study. These results will be correlated with changes in proliferation index induced by different short-term endocrine therapies. We anticipate this will enable us to identify an *endocrine-resistance-breast-cancer-profile*. Additionally we will compare the changes in gene expression in the different study arms; collect blood samples of all patients for research on SNPs in CYP450 sequences; collect blood samples to evaluate whether a change in estradiol concentration correlates with outcome; study the relationship among concentrations of tamoxifenmetabolites in serum/ tumormaterial and expression levels of CYP450 sequences in the tumor; and study changes in estrogenbindingsites induced by short-term endocrine treatment; investigate the effects of IGF-1R and levels of IGF*s on treatment effect; explore the role of DC-SCRIPT in tumor material in relation to

preoperative endocrine exposure. Furthermore, the effect of endocrine therapy on the immunesystem (CD4+ and CD8+ T cells) will be evaluated.

Study design

We will perform a randomized, open-label, multi-institution study. It will compare the efficacy of three different endocrine treatment regimens (Anastrozole, Fulvestrant or Tamoxifen) in changing proliferation-index during a 3 (+/- 1 week) week pre-operative treatment period in breast cancer patients. These results will be correlated to gene expression profiles, phosphorylation status of the ER, SNPs in CYP450 sequences, tamoxifen metabolite concentrations, changes in estrogen serum levels and protein expression patterns.

Intervention

Endocrine therapy during a 3 (+/-1 week) weeks pre-operative treatment period.

Study burden and risks

Once the first informed consent is signed core needle biopsies will be taken of the primary tumor. This biopsy is an extra burden for the participating patient.

The reliability of the sentinel lymph node procedure (SLNP) after pre-operative endocrine therapy is unknown. A false negative rate after full-dose neoadjuvant cytotoxic treatment is around 10%, which is comparable to SLNP without neoadjuvant treatment. As the therapies proposed in this protocol are less intense and shorter in duration we expect no clinical significant risks. Another potential risk could be degradation of ER, due to fulvestrant. To prevent possible tamoxifen insensitivity, all fulvestrant patients shall receive adjuvant an aromatase inhibitor, whenever indicated.

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

• Patients with proven invasive adenocarcinoma of the breast
• Any tumor with a size >= 1cm (NOT inflammatory breast cancer)
Patients with a tumor diameter > 0.5 and < 1.0 cm are eligible when a biopsy can be performed, however for very small tumors leaving behind a radiologic marker need to be discussed.
• WHO-performance score 0 or 1
• Written informed consent

Exclusion criteria

• Clues of metastatic disease by clinical examination according to most recent NABON guidelines
• Multicentric breast cancer
• Inflammatory breast cancer
• Hormone replacement during the last 12 months
• Other systemic treatment during waiting time till surgery
• Already planned date for surgery within the next 2 weeks
• Any psychological, familial, sociological or geographical condition potentially hampering adequate informed consent or compliance with the study protocol
• Patient*s refusal to undergo a core biopsy procedure of the primary tumor before the start of treatment
NB: a concomitant malignancy within the last five years is not an exclusion criterium, because survival is not the primary endpoint. Just as prior invasive breast cancer or DCIS

within the last 15 years is not an exclusion criterium.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2008
Enrollment:	250
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Arimidex
Generic name:	Anastrozole
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Faslodex
Generic name:	Fulvestrant
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Tamoxifen
Generic name:	Tamoxifen
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-03-2008
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	28-11-2008
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-07-2010
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-08-2015
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2008-000644-13-NL
CCMO	NL21855.031.08