CYPTAM study.

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Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23389

Bron
NTR

Verkorte titel
CYPTAM

Aandoening

women with early stage breast cancer
using adjuvant tamoxifen

Dutch:
patientes met vroeg-stadium mammacarcinoom behandeld met adjuvant tamoxifen

Ondersteuning

Primaire sponsor: Leiden University Medical Center (LUMC)
Leiden, the Netherlands
Overige ondersteuning: initiator = sponsor

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

1. To associate CYP2D6 genotype and tamoxifen metabolite plasma concentration to relapse free survival (RFS), disease free survival (DFS) and overall survival (OS) (documentation study).
2. To investigate the effect of a temporary one-step dose escalation of tamoxifen on endoxifen plasma concentration in poor and intermediate metabolizers (pharmacokinetics study).

Amendment: To correlate the CYP2D6 genotype and the serum endoxifen concentrations to the CYP2D6 phenotype determined by a dextromethorphan breath test (DM-BT).

Toelichting onderzoek

Achtergrond van het onderzoek

Tamoxifen is commonly used for the adjuvant treatment of breast cancer.
However, not all women with hormone receptor positive breast cancer benefit from adjuvant tamoxifen. This variable response on tamoxifen may partially be explained by individual differences in biotransformation of tamoxifen to active metabolites.

Tamoxifen is considered a pro-drug and is metabolized to its most active metabolite endoxifen by the hepatic enzyme CYP2D6. Enzymatic activity is highly associated with CYP2D6 genotype. Several - mostly retrospective - studies have associated the poor metabolizer (PM) genotype *4/*4 and the intermediate metabolizer (IM) genotype *1/*4 with worse clinical outcome compared to the extensive metabolizer (EM) genotype *1/*1. However, as some other studies show conflicting results, more and preferably prospective studies are needed. Currently, only the variant *4 allele (being one of the > 80 CYP2D6 alleles known to date) has been investigated in Caucasian populations. Therefore, estimation of the impact of other CYP2D6 genotypes on tamoxifen efficacy is warranted.

Endoxifen plasma concentrations may also be a predictor of tamoxifen response. Previous studies showed significantly lower endoxifen plasma concentrations in poor metabolizers compared to extensive metabolizers, but did not (yet) associate this with outcome. Increasing the administered tamoxifen dose in poor and intermediate metabolizers, may consequently increase endoxifen plasma concentrations and thus tamoxifen response.

Prospective studies may help introduce CYP2D6 genotyping as a tool to tailor hormonal treatment of breast cancer in the future. We started a prospective study that will associate many different CYP2D6 genotypes by Amplichip as well as endoxifen plasma concentration with tamoxifen efficacy.

Amendment: CYP2D6 phenotype was determined by a 13C-dextromethorphan breath test and correlated to the CYP2D6 genotype and endoxifen levels.

Furthermore, we investigated the effect of dose escalation in PMs and IMs on endoxifen levels. The CYPTAM study was therefore subdivided into three different studies:

1. CYPTAM Documentation Study (NEW STATISTICAL ANALYSIS PLAN)

Two blood samples from each participant were collected after >= 2 months of tamoxifen therapy. CYP2D6 genotype and endoxifen plasma concentration were determined and associated with clinical outcome;

2. CYPTAM Pharmacokinetics Study;

3. CYPTAM Phenotyping Study (amendment): One blood sample from each participant of the CYPTAM documentation study were collected after >= 2 months of tamoxifen therapy and endoxifen plasma concentration were determined and associated with CYP2D6 phenotype, determined by a 13C-dextromethorphan breath test. Fifty minutes after ingestion of 0,5 mg/kg 13C-dextromethorphan, patients exhaled in a 1.3 L breath bag. A 13CO2/12CO2 ratio were determined by infrared spectrophotometry. Delta-over-baseline after 50 minutes (DOB50) values were calculated from baseline and postdose 13CO2/12CO2 ratios, reflecting CYP2D6 activity.

All studies require separate informed consent: patients participating in the documentation study were not automatically included in the pharmacokinetics study and phenotyping study.

Doel van het onderzoek

The prodrug tamoxifen is metabolized to its most potent metabolite endoxifen by the enzyme CYP2D6. Up to 25% of Caucasians harbour genetic variants leading to a less active CYP2D6. This may lead to lower endoxifen levels and thus lower tamoxifen efficacy. In the CYPTAM documentation study CYP2D6 genotype and endoxifen concentrations were prospectively related to tamoxifen response in the adjuvant setting. In the CYPTAM pharmacokinetic study, CYP2D6 poor and intermediate metabolizers will temporarily (2 months) receive an escalated tamoxifen dose to investigate the possibility to achieve endoxifen levels similar to those found in CYP2D6 extensive metabolizers.

Onderzoeksopzet

Accrual period is 2 years followed by 2 years of follow-up (mean FU time is 3 years)

Onderzoeksproduct en/of interventie

None:

Tamoxifen is only temporarily (2 months) escalated in a selected group of 12 poor and 12 intermediate metabolizers for pharmacokinetic purposes without expected effect on clinical outcome in the CYPTAM pharmacokinetic study.

Amendment: Only for the CYPTAM phenotyping study: patients receive once 0,5 mg/kg 13C-dextrometorphan. Target number of participants is 200.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Pre- and postmenopausal women who will receive tamoxifen or have already been using tamoxifen during a maximum period of one year, as part of a standard adjuvant therapy for newly diagnosed breast cancer.

2. Willing and able to give written informed consent (separate for documentation and pharmacokinetics study).

3. Age >= 18 years.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Other malignancy within the previous 5 years (except adequately treated in situ carcinoma of cervix or basal cell carcinoma).

2. Hormone receptor negative primary tumors.

Exclusion criteria for PHARMACOKINETICS study only:

1. A medical history of venous thromboembolic events (deep venous thrombosis or pulmonary embolism).

2. Patients who are pregnant or breastfeeding.

3. Patients with a prolonged QT interval on ECG registration.

4. Hemoglobin< 6.0 mmol/L, WBC < 3.0 x 109/L, platelets < 100 x 109/L, bilirubin exceeding normal limits, ASAT and ALAT > 2.5 times the upper limit of normal.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland
Status: Werving gestopt

(Verwachte) startdatum:	01-02-2008
Aantal proefpersonen:	650
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	27-10-2008
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL1448
NTR-old	NTR1509
Ander register	- : P07.234
ISRCTN	ISRCTN wordt niet meer aangevraagd

Resultaten

Samenvatting resultaten
N/A