

CYPTAM study.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON23389

Source

NTR

Brief title

CYPTAM

Health condition

women with early stage breast cancer
using adjuvant tamoxifen

Dutch:

patientes met vroeg-stadium mammacarcinoom behandeld met adjuvant tamoxifen

Sponsors and support

Primary sponsor: Leiden University Medical Center (LUMC)

Leiden, the Netherlands

Source(s) of monetary or material Support: initiator = sponsor

Intervention

Outcome measures

Primary outcome

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).

Secondary outcome

1. To evaluate tamoxifen toxicity in patients participating in dose escalation

Third Amendment: Statistical Analysis Plan for the documentation study.

Secondary objectives:

1. To associate endoxifen concentrations to disease-free survival (DFSt), overall survival (OS), relapse-free survival complete (RFSc) and disease-free survival (DFSc).

2. To associate CYP2D6 predicted phenotype to DFSt, OS, RFSc and DFSc.

- DFSt was defined as the time from study enrolment until loco-regional or distant recurrence or second breast cancer or death without recurrence. In case of a subsequent switch to an aromatase inhibitor, patients were censored at the time of tamoxifen discontinuation.

- OS was defined as the time from study enrolment until death by any cause.

- RFSc was defined as the time from study enrolment until loco-regional or distant recurrence or second breast cancer. In case of a subsequent switch to an aromatase inhibitor, patients were not censored at the time of tamoxifen discontinuation, but the complete period until an event or lost to follow-up was used.

- DFSc was defined as the time from study enrolment until loco-regional or distant recurrence or second breast cancer or death without recurrence. In case of a subsequent switch to an aromatase inhibitor, patients were not censored at the time of tamoxifen discontinuation, but the complete period until an event or lost to follow-up were used.

Study description

Background summary

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 ^{13}C -dextromethorphan breath test. Fifty minutes after ingestion of 0,5 mg/kg ^{13}C -dextromethorphan, patients exhaled in a 1.3 L breath bag. A $^{13}\text{CO}_2/^{12}\text{CO}_2$ ratio were determined by infrared spectrophotometry. Delta-over-baseline after 50 minutes (DOB50) values were calculated from baseline and postdose $^{13}\text{CO}_2/^{12}\text{CO}_2$ 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.

Study objective

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.

Study design

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

Intervention

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 ^{13}C -dextromethorphan. Target number of participants is 200.

Contacts

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Eligibility criteria

Inclusion criteria

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 \geq 18 years.

Exclusion criteria

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.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	01-02-2008
Enrollment:	650
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion	
Date:	27-10-2008
Application type:	First submission

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
NTR-new	NL1448
NTR-old	NTR1509
Other	- : P07.234
ISRCTN	ISRCTN wordt niet meer aangevraagd

Study results

Summary results

N/A