Predicting an accurate tamoxifen dose: a feasibility study in patients with hormone positive breast cancer

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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-OMON53836

Source
ToetsingOnline

Brief title
the PREDICTAM study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mammacarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: breast cancer, modelling, prediction, tamoxifen

Outcome measures

Primary outcome

The primary endpoint is the proportion of patients that reach an endoxifen level of 16 nmol/L or higher after three months of tamoxifen treatment. The main study parameter is the endoxifen level at 3 months after baseline.

Secondary outcome

1. The total success rate of the POP-PK model as well as in different groups, stratified by dosage as predicted by the POP-PK model.

2. The predictive value of the POP-PK model for patients who do not reach the 16 nmol/L endoxifen threshold with the highest prescribed tamoxifen dose of 40 mg;

3. The correlation between the endoxifen values from an early blood sample (at baseline and 4-6 weeks after baseline) and the steady-state concentration of endoxifen;

4. The difference in incidence of side-effects and quality of life between baseline and 3 months after tamoxifen treatment as determined by FACT-ES questionnaires.

5. The intra-patient difference in cognitive test performance and self-reported cognition between baseline and after two years of tamoxifen treatment.

6. The association between tamoxifen, dose, plasma concentrations of tamoxifen and endoxifen and intra-patient differences in cognitive test performance and

self-reported cognition.

Study description

Background summary

Adjuvant treatment with tamoxifen is the standard of care for women with estrogen receptor positive (ER+) breast cancer. Tamoxifen is converted to endoxifen, its active metabolite, via CYP2D6 enzymes. The literature states that an endoxifen concentration of at least 16 nmol/L is needed to produce a therapeutic effect. Therapeutic Drug Monitoring (TDM) has been proven to be a successful technique to reach the 16 nmol/L endoxifen threshold after 6 months. However, in general TDM can only be used when a drug is in steady-state, which for endoxifen is reached after 3 months for normal metabolizers. For poor- and intermediate metabolizers, the time until steady-state is presumably even longer. This could possibly result in undertreatment within the first 3 to 6 months of tamoxifen treatment. In this study, model-informed precision dosing (MIPD) will be used to counter this problem. The Pharmacokinetic-model, which is used for MIPD, includes CYP2D6 genotype, co-medication, age, body height, BMI and CYP2D6/CYP3A inhibitor use to predict a patient tailored dose. Using MIPD, our aim is to decrease the proportion of patients that are undertreated within the first three months of tamoxifen treatment.

Study objective

The primary objective of this study is to determine the proportion of patients that reach an endoxifen level of 16 nmol/L or higher using MIPD.
Secondary objectives:
1. To determine the total success rate of the POP-PK model as well as in different groups, stratified by dosage as predicted by the POP-PK model.
2. To establish the predictive value of the POP-PK model for patients which will not reach the 16 nmol/L endoxifen threshold with the highest prescribed tamoxifen dose of 40 mg.
3. To test if an early blood sample (at baseline and 4-6 weeks after baseline) is indicative for the steady-state concentration;
4. To compare the incidence of side-effects and quality of life of breast cancer patients between baseline and the final assessment after 3 months
5. To investigate change in objective cognitive functioning, measured by a validated online cognitive test (Amsterdam Cognition Scan), and subjective cognitive functioning, measured by a validated questionnaire, between the start of tamoxifen treatment and two years after start of tamoxifen treatment
6. To investigate the association between tamoxifen dose, tamoxifen plasma concentrations and endoxifen plasma concentrations and change in objective and

subjective cognitive functioning.

Study design

This is a non-randomized, single-center, single-arm, MIPD intervention study. The control arm will be provided by the TOTAM study (METC: 2017543/NTR: NL6918).

Intervention

At baseline, CYP2D6 genotype, BMI and body height will be measured. Additionally, information about concomitant CYP2D6 and CYP3A inhibitor use and age will be collected. Based on these predictors, a patient-tailored tamoxifen dose will be predicted at baseline using a POP-PK model. This tamoxifen dose can either be 20, 30 or 40 mg. Patients will be seen in the out-patient clinic for pharmacokinetic blood sampling at baseline, after 4-6 weeks and after 3 months. The tamoxifen and endoxifen levels after three months will be used to assess the primary and secondary outcomes. At baseline, patients will be asked to complete a cognition test.

Study burden and risks

This study may provide a more personalized adjuvant tamoxifen therapy for breast cancer patients. Therefore, patients could benefit individually by reaching adequate levels sooner. Over the course of the study, three blood samples will be taken from each individual patients. The risks of these blood samples are considered low. Additionally, the dose of 30 or 40 mg tamoxifen at baseline may cause more side-effects than the standard dose of 20 mg tamoxifen. However, prospective studies have shown no correlation between tamoxifen dose and incidence of side effects. Therefore, these risks are also considered low

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Age >= 18 years;
2. WHO Performance Status <= 1
3. Patients with primary breast cancer, with a prescription for adjuvant tamoxifen treatment.
4. Willing to abstain from strong and moderate CYP3A4 or CYP2D6 inhibitors or inducers, according to: CYTOCHROME P450 DRUG INTERACTION TABLE - Drug Interactions (iu.edu);
5. Able and willing to sign the Informed Consent Form;
6. Able and willing to undergo blood sampling for PK analysis.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Patients with known alcoholism, drug addiction and/or psychiatric or physiological condition which in the opinion of the investigator would impair treatment compliance;
2. > 2 weeks of tamoxifen treatment before inclusion
3. Patients who*s endoxifen levels have been used for therapeutic drug monitoring in the past.
4. Evidence of a neurological disorder which might affect cognitive functioning (only for cognition scan part)

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2022
Enrollment:	115
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Nolvadex
Generic name:	Tamoxifen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-08-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	14-11-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	30-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2022-002426-28-NL
CCMO	NL81896.078.22