PharmacoKINEtics of TAMoxifen and its metabolites in breast cancer patients: the influence of a dose increase in phenotypic poor metabolizers of CYP2D6 (KINETAM)

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Primary: To evaluate the effect of a dose increase to 40mg tamoxifen QD for 4 weeks in patients with at least one CYP2D6 variant allele and/or the presence of a CYP2D6 inhibitorSecondary:To evaluate the effect of concomitant use of (potential)...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast disorders
Study type	Interventional

Summary

ID

NL-OMON34869

Source
ToetsingOnline

Brief title
KINETAM

Condition

- Breast disorders

Synonym
breast cancer; mamma carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: breast cancer, pharmacokinetics, poor metabolizers of CYP2D6, tamoxifen

Outcome measures

Primary outcome

Cmin plasma concentrations of tamoxifen and its metabolites after 4 weeks of

dosing with 40mg QD tamoxifen (compared to baseline: 20mg QD tamoxifen).

Secondary outcome

Influence of CYP2D6 inhibitors/polymorphism on pharmacokinetics of tamoxifen

and metabolites in breast cancer patients.

Study description

Background summary

Although already some information is available on the importance of CYP2D6 polymorphisms and/or the use of CYP2D6 inhibitors as co-medication that may influence the treatment outcome of tamoxifen, this information does currently not lead to a change in the management of this patient population. All women on tamoxifen receive the standard dose of 20mg QD, irrespective of the use of potential CYP2D6 inhibitors, and are not tested for CYP2D6 polymorphisms prior to start of tamoxifen treatment.

Possible explanations (in random order) for this apparent discrepancy are:
- Conflicting results from the various studies on the importance of CYP2D6 polymorphisms and CYP2D6 inhibitors
- Few or no information on the actual plasma levels of endoxifen in these studies
- Use of CYP3A inhibitors not taken into account (see figure 1)
- The relative potency of CYP2D6 inhibitors has not been formally assessed, let alone its influence on tamoxifen pharmacokinetics.
- Other factors that may influence tamoxifen activation are usually not

included in the analyses, such as body weight, adherence, etc. For instance, patients with depression could be less adherent, and therefore benefit less from tamoxifen treatment; this effect could be unrelated to the use of antidepressants in these women.
- Any factor that might be important is usually only studied as a single determinant; for instance, we are aware of only one study in 80 women that has looked at both CYP2D6 and use of CYP2D6 inhibitors simultaneously [6].
- Most importantly, to our knowledge, no information is available that dose adjustments in women who are phenotypically poor metabolizers of tamoxifen can compensate for reduced formation of endoxifen

In an attempt to at least resolve some of these issues we propose a prospective study in women taking tamoxifen at a dose of 20mg QD who are being followed at several large oncology clinics in the south-eastern part of the Netherlands (Nijmegen (CWZ & Radboud), Den Bosch, Harderwijk and Arnhem). In each woman, information will be collected on endoxifen levels, CYP2D6 status, adherence and use of co-medication. In women who are phenotypically poor metabolizers of tamoxifen, a dose increase to 40mg QD will be applied and the effect of this intervention on tamoxifen pharmacokinetics will be evaluated after 4 weeks.

Study objective

Primary:
To evaluate the effect of a dose increase to 40mg tamoxifen QD for 4 weeks in patients with at least one CYP2D6 variant allele and/or the presence of a CYP2D6 inhibitor

Secondary:
To evaluate the effect of concomitant use of (potential) CYP2D6 inhibitors/polymorphisms on the pharmacokinetics of tamoxifen and its metabolites in breast cancer patients

Study design

This is an open-label, cross-sectional, multi-centre, phase-I, trial in 150 women who are being treated with tamoxifen 20mg QD.

After meeting the inclusion criteria and passing the exclusion criteria, subjects will be sampled to determine the CYP2D6 status and plasma endoxifen levels. Co-medication and adherence will be recorded based on the patient*s information. In case of questions about the co-medication, and after approval of the patient, the patient*s pharmacy will be contacted.

In case a CYP2D6 polymorphism and/or the presence of a CYP2D6 inhibitor is found, a dose increase to tamoxifen 40mg QD will be applied and the patient will return for measurement of the plasma endoxifen level 4 weeks later. After

this visit the patient can continue taking the normal dose (20 mg) of tamoxifen.

Intervention

In case a CYP2D6 polymorphism and/or the presence of a CYP2D6 inhibitor is found, a dose increase to tamoxifen 40mg QD will be applied and the patient will return for measurement of the plasma endoxifen level 4 weeks later. After this visit the patient can continue taking the normal dose (20 mg) of tamoxifen.

Study burden and risks

Patients may experience side-effects of a higher dose of tamoxifen than they are use to using.
Venapuncture may cause discomfort and/or pain.

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

1.Subject is at least 18 years at screening
2. Subject is able and willing to sign the Informed Consent Form prior to screening evaluations.
3. Subject is a female patient with (a history of) breast cancer; has been treated with tamoxifen 20mg QD for at least 4 weeks and is expected to be treated for at least another 4 weeks.

Exclusion criteria

1. Inability to understand the nature and extent of the trial and the procedures required.
2. Participation in a drug trial within 60 days prior to the first dose.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-07-2010
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Nolvadex
Generic name:	tamoxifen
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-03-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-06-2010
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2010-019065-29-NL
CCMO	NL31814.091.10