Study on the pharmacokinetic interaction between diclofenac and tamoxifen in patients with breast cancer. "the DICLOTAM study"

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Primary objective1. To compare the Area under the curve (AUC) of endoxifen in patients with breast cancer treated with tamoxifen with and without diclofenac.Secondary objectives1. To compare the Area under the Curve (AUC) of tamoxifen and endoxifen-...

Ethical review	Not approved
Status	Will not start
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON48096

Source
ToetsingOnline

Brief title
DICLOTAM study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Hormone sensitieve breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Stichting die oncologie onderzoek support

Intervention

Keyword: Diclofenac, Drug-Drug Interaction, Pharmacokinetics, Tamoxifen

Outcome measures

Primary outcome

To investigate the interaction between diclofenac and tamoxifen; by comparing the Area under the curve (AUC) of endoxifen in patients with breast cancer treated with tamoxifen with and without diclofenac.

Secondary outcome

1. To compare the Area Under the Curve (AUC) of tamoxifen and endoxifen-glucuronide in patients with breast cancer treated with tamoxifen with and without diclofenac.

2. To compare other tamoxifen, endoxifen-glucuronide and endoxifen pharmacokinetic outcomes (i.e. clearance, maximum concentration (Cmax), minimal concentration (Ctrough) and time until maximum concentration (Tmax) and elimination half-life (T*)). Furthermore the endoxifen/endoxifen-glucuronide ratio in patients with breast cancer treated with tamoxifen with and without diclofenac.

3. To evaluate the incidence and severity of side-effects of treatment with tamoxifen in absence and presence of diclofenac.

Study description

Background summary

Nowadays many (cancer) patients use additional medication next to their anti-cancer therapy. Thereby increasing the risk of possible severe drug-drug interactions ultimately leading to a suboptimal therapeutic outcome or an increase in toxicity. One of the most commonly used class of drugs are the Non-Steroid Anti-Inflammatory Drugs (NSAIDs). NSAIDs are used in the treatment of fever, pain and inflammation. Approximately 18% of cancer patients use NSAIDs for several conditions and therefore this class of drugs belong to one of the most prescribed drugs in the Netherlands, with diclofenac as the most commonly used NSAID. The drug-interaction potential of NSAIDs is considered low in general, although most NSAIDs are substrates for CYP2C9 and therefore might not be combined with strong CYP2C9 inhibitors or inducers. However several in vitro studies show inhibitory potential of NSAIDs on phase II drug metabolism. Phase II drug metabolism plays an important role in the metabolism of several drugs. Through several conjugating enzymes (e.g. UDP-glucuronosyltransferases (UGT), sulfotransferases (SULT), glutathione S-transferases) active drugs will be transformed into pharmacologically mostly inactive excretable forms. UGT is one of the main phase II metabolizing enzymes, with UGT2B7, UGT1A1 and UGT1A4 as the most important enzymes. In contrast to drug-drug interactions regarding phase I metabolism less is known about drug-drug interactions regarding phase II drug metabolism. In theory, inhibition or induction of these phase II (e.g. UGT) enzymes can lead to significantly altered plasma concentration of phase II substrate drugs. For example, a clinical study with the NSAID mefenamic acid showed a significant 51% increase in dapagliflozin exposure through UGT1A9 inhibition.5 One of the most potent and well known inhibitors of several UGT*s (e.g. UGT1A4, UGT2B7, UGT1A3, UGT1A6, UGT1A1 and UGT1A9), according to in vitro evidence, is diclofenac. Therefore making diclofenac a potential drug causing severe drug-drug interactions.

Study objective

Primary objective

1. To compare the Area under the curve (AUC) of endoxifen in patients with breast cancer treated with tamoxifen with and without diclofenac.

Secondary objectives

1. To compare the Area under the Curve (AUC) of tamoxifen and endoxifen-glucuronide in patients with breast cancer treated with tamoxifen with and without diclofenac.
2. To compare other tamoxifen, endoxifen-glucuronide and endoxifen pharmacokinetic outcomes (i.e. clearance, maximum concentration (Cmax), minimal

concentration (Ctrough) and time until maximum concentration (tmax) and elimination half-life (t*)). Furthermore the endoxifen/endoxifen-glucuronide ratio will be determined in patients with breast cancer treated with tamoxifen with and without diclofenac.
3. To evaluate the incidence and severity of side-effects of treatment with tamoxifen in absence and presence of diclofenac.

Study design

This is an open label 2 period exploratory, randomized, single-center, pharmacokinetic cross-over study in patients taking tamoxifen for the treatment of breast cancer. This study will be performed in the Erasmus MC Cancer Institute in Rotterdam, the Netherlands. It is anticipated that the study will be performed within a 1 year period after approval by the ethical board. A total of 14 evaluable patients need to be enrolled to reach the primary endpoint. Before entering the study patients need to be on steady state endoxifen plasma levels. To reach steady state patients have to use tamoxifen (at the same dose) for at least three months (run-in phase). After reaching steady-state patients will use tamoxifen (phase A) alone or tamoxifen concomitantly with diclofenac (phase B) in this order or vice versa depending on randomization. Patients must use diclofenac 75 mg twice daily concomitantly with tamoxifen for 7 consecutive days. On the 7th and 14th day of the study patients will be hospitalized for pharmacokinetic blood sampling depending on the randomization sequence.

Intervention

Tamoxifen will be used as standard care of treatment (adjuvant and metastatic setting). Tamoxifen is given in a dosage of 20-40 mg q.d. Dose modifications are not allowed after the run-in phase of three months. Tamoxifen will be administered for at least three months at the same dose to guarantee steady-state of endoxifen. Patients will use the same brand of tamoxifen during the whole study period. Tamoxifen will be administered daily at approximately 10.00AM. Diclofenac will be given in a dosage of 75 mg twice daily dose concomitantly with tamoxifen at 10.00 AM and 10:00 PM. On PK-days a light meal exactly 2 hours before tamoxifen treatment is permitted.

Study burden and risks

Patients will be invited to the hospital for a total of 2 days, during the visits pharmacokinetic blood withdrawals will be performed.
Minor risks to be expected are side effects of tamoxifen or diclofenac for which patients will be observed carefully.

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. Age * 18 years
2. Patients with a confirmed diagnosis of primary or advanced breast cancer, who are on tamoxifen treatment for at least three months (steady state concentration).
3. WHO performance * 1 (see Appendix B)
4. Able and willing to sign the informed consent form prior to screening evaluations
5. Willing to abstain from strong CYP3A4, CYP2D6, CYP2C9/2C19, UGT and P-gp inhibitors or inducers, herbal or dietary supplements or other over-the-counter medication besides paracetamol.
6. Adequate organ function defined as:
- ALAT and ASAT <5.0 upper limit of normal (ULN)
- bilirubin <1.5 (ULN)
- GFR > 30 ml/min/1.73 m2

- Controlled thyroid dysfunction

Exclusion criteria

1. Pregnant or lactating patients
2. Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria)
3. Patients with a history of (stomach) ulcers or gastric bleeding or hypersensitivity to NSAIDs.
4. Known serious illness or medical unstable conditions that could interfere with this study requiring treatment (e.g. HIV, hepatitis, Varicella zoster or herpes zoster, organ transplants, kidney failure (GFR<60 ml/min/1.73 m2), serious liver disease (e.g. severe cirrhosis), cardiac and respiratory diseases)
5. A CYP2D6 poor metabolizer or ultra-rapid metabolizer phenotype based on CYP2D6 genotyping outcome.

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	14
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Diclofenac

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

Ethics review

Approved WMO Date:	09-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Not approved Date:	02-04-2019
Application type:	First submission
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	EUCTR2018-003482-33-NL
CCMO	NL68151.078.18