The effect of curcumin and piperine on the pharmacokinetics of tamoxifen in patients with breast cancer *the ELDORADO study*

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON43321

Source
ToetsingOnline

Brief title
The ELDORADO-study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Curcumin, Pharmacokinetics, Piperine, Tamoxifen

Outcome measures

Primary outcome

To determine the influence of curcumin with or without piperine, in patients with breast cancer, on endoxifen plasma pharmacokinetics. The main parameter will be AUC.

Secondary outcome

1. Other pharmacokinetic outcomes (i.e. clearance, minimum concentration (Ctrough) and the tamoxifen/endoxifen ratio.

2. To evaluate plasma concentration levels of tamoxifen and other tamoxifen metabolites

3. To evaluate the incidence and severity of side-effects of treatment with tamoxifen in absence and presence of curcumin with or without piperine.

Study description

Background summary

Nowadays lots of cancer patients use herbal medicine. One of the most popular herb drugs is curcumin. Curcumin is often used as additional therapy next to normal clinical practice. Curcumin might influence pharmacokinetics of several drugs due to inhibition of several cytochrome P450 enzymes such as CYP3A4 and CYP2D6. It also influences UGT and several in- and efflux pumps such as P-glycoprotein and OATP.

An example of a drug, which metabolism depends on this enzymes and pumps is tamoxifen, an estrogen receptor antagonist used by breast cancer patients . Since curcumin may alter the exposure, and thereby, tamoxifen efficacy it is

important to investigate the clinical significance of this food-drug interaction.

Because of its low bioavailability curcumin is often administered concomitantly with piperine, an extract of black pepper. Piperine may increase bioavailability by inhibition of glucoronidation of curcumin and thereby potentially increases the effect of curcumin on tamoxifen pharmacokinetics. Furthermore piperine is believed to have an effect on several metabolizing enzymes such as CYP 3A4, CYP2C9 and CYP2B6.

The main objective of this study is to evaluate the pharmacokinetics (PK) of tamoxifen, when concomitantly used with curcumin with or without piperine in patients with breast cancer.

Study objective

The main objective is: To determine the influence of curcumin with or without piperine, in patients with breast cancer, on endoxifen plasma pharmacokinetics (AUC).

Secundary objectives are:
1. Other pharmacokinetic outcomes (i.e. clearance, minimum concentration (Ctrough) and the tamoxifen/endoxifen ratio.
3. To evaluate plasma concentration levels of tamoxifen and other tamoxifen metabolites
2. To evaluate the incidence and severity of side-effects of treatment with tamoxifen in absence and presence of curcumin with or without piperine.

Study design

This is an open label three period exploratory, randomized, cross-over study in patients taking tamoxifen for breast cancer. This study will be performed at the Erasmus MC Cancer Institute in Rotterdam, The Netherlands. It is anticipated that the study will be performed within a 1 year study period after approval by the institutional ethical board. Before entering the study patients have to be on steady state tamoxifen plasma levels. To reach steady state patients have to use tamoxifen (at the same dose) for at least 28 days (run-in phase).

After reaching steady-state all patients will use tamoxifen alone (phase A) or with curcumin with or without piperine (phase B and phase C, respectively). Patients must use curcumin with or without piperine for at least 28 days to ensure steady-state concentration of curcumin.
Patients will be randomized in two sequence groups, sequence ABC or sequence CBA to rule out any sequence effects. Patients will be hospitalized on day 28, 56 and 84 for PK blood sampling for 24 hours (PK1, PK2, PK3).

Intervention

Patients will be treated with tamoxifen only and in combination with curcumin with or without piperine.

Study burden and risks

Patients will be admitted to the hospital for a total of three days, during which pharmacokinetic blood withdrawals will be performed. Patients will be randomized into 2 sequence groups consisting of 3 phases. In 2 phases patients are also treated with curcumin with or without piperine for 28 consecutive days. Patients do not benefit individually from this study. Major risks to be expected are side effects of tamoxifen or curcumin and piperine for which patients will be carefully observed.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
Rotterdam 3015CE
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

's-Gravendijkwal 230
Rotterdam 3015CE
NL

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. Histological or cytological confirmed diagnosis of breast cancer in patients with an indication for tamoxifen treatment.;3. WHO Performance Status * 1 ;4. Able and willing to sign the Informed Consent Form prior to screening evaluations;5. Abstain from curry, grapefruit (juice), (herbal) dietary supplements besides curcumin, herbals, over-the-counter medication (except for paracetamol and ibuprofen).;6. Adequate baseline patient characteristics (complete blood count, and serum biochemistry which involves sodium, potassium, creatinin, calculation of creatinin clearance (MDRD), AST, ALT, gamma glutamyltranspeptidase (GGT), lactate dehydrogenase (LDH), ALP, total bilirubin, albumin).

Exclusion criteria

1. Pregnant or lactating patients.;2. Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria).;3. Use of other drugs, which are mainly dependent for their metabolism on CYP3A4 and CYP2D6. ;4. Known serious illness or medical unstable conditions that could interfere with this study; requiring treatment (e.g. infection, bleedings, uncontrolled hypertension despite optimal medical management, HIV, hepatitis, organ transplants, kidney, cardiac and respiratory diseases).;5. Bilirubin CTCAE grade 2 or higher, ASAT/ALAT CTCAE grade 2 or higher and grade 3 or higher in patients with liver metastasis. . Renal function impairment CTCAE grade 2 or higher.;6. Symptomatic CNS metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent.;7. Known hypersensitivity to any of the study drugs, study drug classes, or excipients in the formulation. ;8. Patients on strong CYP3A4 or CYP2D6 inhibitors or inducers, P-gp substrates or medication or supplements which can interact with tamoxifen and curcumin are not eligible for the study.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-02-2017
Enrollment:	16
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	23-11-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2017
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	EUCTR2016-004008-71-NL
CCMO	NL59496.078.16

Study results

Date completed:	24-04-2018
Actual enrolment:	17