Study on the possible pharmacokinetic interaction between grean tea supplements and tamoxifen in patients with breast cancer. "the TEA study"

Published: 27-08-2019
Last updated: 10-04-2024

Primary objective:1. To compare the change from baseline of the Area under the curve (AUC) of tamoxifen in patients with breast cancer treated with tamoxifen with and without green tea supplements.Secondary objectives:1. To compare the Area under...

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

Summary

ID

NL-OMON48342

Source
ToetsingOnline

Brief title
TEA study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Hormone sensitive breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Erasmus MC

Intervention

Keyword: Food-Drug Interaction, Green tea, Pharmacokinetics, Tamoxifen

Outcome measures

Primary outcome

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

Secondary outcome

1. To compare the Area Under the Curve (AUC) of tamoxifen in patients with breast cancer treated with tamoxifen with and without green tea capsules.

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

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

Study description

Background summary

Tamoxifen is an effective oral estrogen receptor (ER) antagonist with relatively mild side-effects for the treatment of ER positive breast cancer. Nowadays many (cancer) patients often use additional herbs or supplements next to their anti-cancer therapy. Besides the believed positive effects of these supplements, the risk of possible severe drug-drug interactions ultimately leading to diminished therapeutic outcomes or an increase in toxicity is also increased. One of the most popular supplements used by cancer patients is green tea. Green tea is believed to have anti-cancer effects due to catechins,

a class of flavonoids that exert potent antioxidant activity, of which (-)-epigallocatechin-3-gallate (EGCG) has the highest antioxidant potential.

Several in vitro studies suggest inhibition by green tea supplements of several phase I metabolizing enzymes like CYP3A4 and CYP2D6 and inhibition of several drug-transporters among which the efflux transporter P-glycoprotein (P-gP) and several influx-transporters like organic anion transporting polypeptides (OATP). EGCG significantly increased the bioavailability of several drugs like verapamil, simvastatin, 5-fluoruracil and diltiazem in rat studies.

After absorption tamoxifen is metabolized mainly by CYP3A4 and CYP2D6 in several (active) metabolites of which endoxifen is the most important. Tamoxifen, like many anti-cancer drugs, relies on phase II metabolism before they can be excreted from the body. Endoxifen is ultimately glucuronidated into endoxifen-glucuronide mainly by UGT1A8 and UGT1A10. Since tamoxifen has a complex metabolism, it is prone to drug-drug interactions with herbs and supplements as was shown previously with curcumin. Furthermore, a study in rats demonstrated a significant 43% increase in AUC of tamoxifen when treated with green tea supplements suggesting P-glycoprotein (P-gP) and CYP3A4 inhibition or improved tamoxifen absorption.

Since many patients use green tea supplements in addition to their anticancer therapy a drug-drug interaction, resulting in increased (better absorption and inhibition efflux pump) or decreased (OATP1B1 inhibition) tamoxifen and endoxifen concentrations, and therefore may have serious clinical impact in these cancer patients.
Furthermore a clinical study in human demonstrated significant inhibition of the organic anion transporting polypeptide 1A2 (OATP1A2), which acts as an influx transporter in the gut, with 700 mL green tea with a high amount of catechins (1.54 mg/mL) leading to 85% decrease in exposure to the OATP1A2 substrate nadolol. Green tea supplements appears to be a substance with a high interaction potential in the clinical setting and therefore may deprive patients from optimal therapy or increase therapy related side-effects.

Study objective

Primary objective:

1. To compare the change from baseline of the Area under the curve (AUC) of tamoxifen in patients with breast cancer treated with tamoxifen with and without green tea supplements.

Secondary objectives:

1. To compare the Area under the Curve (AUC) of endoxifen in patients with breast cancer treated with tamoxifen with and without green tea.
2. To compare other tamoxifen and endoxifen pharmacokinetic outcomes (i.e.

clearance, maximum concentration (Cmax), minimal concentration (Ctrough) and time until maximum concentration (tmax) and elimination half-life (t*)). in patients with breast cancer treated with tamoxifen with and without green tea.
3. To evaluate the incidence and severity of side-effects of treatment with tamoxifen in absence and presence of green tea.

Study design

This is a 2-period, randomized, cross-over pharmacokinetic study.

Intervention

Fourteen patients on steady-state tamoxifen treatment will be randomised into two different sequences. Depending on which randomization sequence patients will start with tamoxifen alone (sequence AB) followed by tamoxifen with green tea supplements for 14 consecutive days or vice versa (sequence BA). Patients will be admitted to the hospital for 24-hour blood sampling on days 14 and 28 of the study for pharmacokinetic analysis.

Study burden and risks

Patients with breast cancer will be treated with tamoxifen as standard of care. Patients consented for this study will be randomised into 2 sequence groups consisting of 2 phases. In phase A patients will only use tamoxifen and in phase C patients will use tamoxifen concomitantly with green tea capsules for 14 consecutive days. During the 24 hour pharmacokinetic measurement, patients are admitted to the hospital twice for an overnight stay (2 times 24 hours), during which 13 pharmacokinetic blood withdrawals of 6 mL will be performed. Major risks are not expected for tamoxifen, as tamoxifen is registered as standard of care. Since green tea is given for a short period of time (14 days), no major risks are to be expected. Nonetheless, we will carefully observe all included patients using a patient diary and two-weekly phone or clinical appointment, during the whole study period.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

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

's Gravendijkwal 230
Rotterdam 3015 CE
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. 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
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. Willing to abstain from a cup of green tea (<4 h after tamoxifen intake)

Exclusion criteria

1. Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria)
2. Patients with an active gastric ulcer
3. 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<30 ml/min/1.73 m2), serious liver disease (e.g. severe cirrhosis), cardiac and respiratory diseases)
4. A CYP2D6 poor metabolizer or ultra-rapid metabolizer phenotype based on

CYP2D6 genotyping outcome

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-10-2019
Enrollment:	14
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:	27-08-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	07-10-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR201900291037 -NL
CCMO	NL70776.056.19