Study on the possible pharmacokinetic interaction between green tea supplements and tamoxifen in patients with breast cancer. “the TEA study”

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21997

Source
Nationaal Trial Register

Brief title
TEA

Health condition

Breast cancer

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: Erasmus MC Cancer Institute

Intervention

Outcome measures

Primary outcome

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 outcome

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 (t½)). 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

Rationale: Tamoxifen is an effective oral estrogen receptor (ER) antagonist with relatively mild sideeffects for the treatment of ER positive breast cancer. Nowadays many (cancer) patients often use additional herbs or supplements in combination with 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 nowadays is green tea. Green tea is believed to have anti-cancer effects resulting from catechins, a class of flavonoids that exert potent antioxidant activity, of which (-)-epigallocatechin-3-gallate (EGCG) has the highest antioxidant potential. However, as shown previously with curcumin, conventional medication may have influence on the pharmacokinetics of several anti-cancer drugs like tamoxifen.

Several studies suggest inhibition by green tea supplements of several phase I metabolizing enzymes like CYP3A4 and CYP2D6 and inhibition of several transporters among which the efflux transporter P-glycoprotein (ABCB1). EGCG significantly increased the bioavailability of several drugs like verapamil, simvastatin, 5-fluoruracil and diltiazem in rat studies. Furthermore, a clinical study in human demonstrated significant inhibition of the organic anion transporting polypeptide 1A1 (OATP1A1) 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 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.

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 and may therefore alter tamoxifen exposure.

Since many patients use green tea supplements in addition to their anticancer therapy a drug-drug interaction, may result in increased or decreased tamoxifen and endoxifen concentrations, and therefore may have serious clinical impact in these cancer patients. Objective: To determine the influence of concomitant administration of tamoxifen and green tea supplements on tamoxifen and endoxifen plasma concentrations Study design: This is a 2-period, randomized, cross-over pharmacokinetic study. Study population: Patients (≥18 years of age) with breast cancer treated with tamoxifen Intervention (if applicable): 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 ABC) followed by tamoxifen with green tea supplements for 14 consecutive days or vice versa (sequence CBA). Patients will be admitted to the hospital for 24-hour blood sampling on days 14 and 42 of the study for pharmacokinetic analysis. Main study parameters/endpoints: The primary endpoint of this study is the change from baseline of the Area Under the Curve (AUC) of endoxifen. The AUC of endoxifen during tamoxifen monotherapy will be compared to the AUC of endoxifen during concomitant treatment of tamoxifen with green tea supplements. Secondary endpoints include the difference in AUC for tamoxifen and other pharmacokinetic parameters of endoxifen, tamoxifen (i.e. clearance, maximum concentration (Cmax), minimal concentration (Ctrough) and time until maximum concentration (tmax) and elimination half-life (t½)). Furthermore, an explorative analysis on differences in side-effects per treatment phase will be performed. Nature and extent of the burden and risks associated with participation, benefit and group relatedness: 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.

Study objective

After absorption tamoxifen is metabolized by CYP3A4 and CYP2D6 in several (active) metabolites of which endoxifen is the most important.(11) 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 as was shown previously with curcumin.(7) Furthermore a study in rats demonstrated a significant 43% increase in AUC of tamoxifen when treated with green tea supplements suggesting

Pglycoprotein and CYP3A4 inhibition.(12)

As mentioned earlier green may also inhibit several drug transporters among which P-gp and OATP. A clinical study in patients using nadolol showed a 85% decrease in nadolol exposure due to significant inhibition by green tea.(10) The main transporter involved in the absorption and excretion of tamoxifen is OATP1B1.(11) In vitro results suggest an inhibitory effect on this transporter together with other drug-transporters (e.g. OCT1, MATE1, P-gp). (13) Therefore, making green tea a possible agent which may influence tamoxifen exposure. Since many patients use green tea in addition to their anticancer therapy a drug-drug interaction may have serious clinical impact in these patients.

Study design

Q4 2021

Intervention

Green tea supplements

Contacts

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Eligibility criteria

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. (see Appendix C)
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. Patients with a BMI >35 kg/m2
4. Age >80 years
5. 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)
6. A CYP2D6 poor metabolizer or ultra-rapid metabolizer phenotype based on CYP2D6 genotyping outcome
7. Use of strong CYP3A4, CYP2D6, CYP2C9/2C19, UGT and P-gp inhibitors or inducers , herbal or dietary supplements or other over-the-counter medication besides paracetamol (e.g. Veregen, grapefruit, st. Johns-wort)

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-10-2019
Enrollment:	14
Type:	Actual

IPD sharing statement

Plan to share IPD: Yes

Ethics review

Positive opinion

Date:	11-11-2019
Application type:	First submission

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
NTR-new	NL8144
Other	Erasmus MC Cancer Institute : MEC 2019-0581

Study results