Optimizing endoxifen concentration through the induction of CYP3A4, CYP2C and CYP2D6 mediated tamoxifen metabolism

Published: 18-01-2011
Last updated: 04-05-2024

- To examine the effects of cytochrome P450 induction by rifampicin on the metabolism and pharmacokinetics of tamoxifen and its metabolites. Induction of cytochrome P450 enzyme expression (including CYP3A4, CYP2C and CYP2D6) by rifampicin will...

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

Summary

ID

NL-OMON38337

Source
ToetsingOnline

Brief title
Induction of tamoxifen metabolism

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: CYP2D6, enzyme induction, Rifampicin, Tamoxifen

Outcome measures

Primary outcome

Amendment:

N.A. (cancelled)

Secondary outcome

Amendment:

- To validate the previously developed dextromethorphan phenotyping test (AUC

0-6h).

Study description

Background summary

Tamoxifen therapy has proven its efficacy over the last decades. However, 30-50% of the patients with adjuvant tamoxifen therapy experience a relapse or even die as a consequence of breast cancer, which indicates individual differences in response to tamoxifen therapy. Which patients will respond to therapy and which patients are prone to develop tamoxifen-related side-effects is largely unknown prior to therapy, which makes it important to develop good predictive markers.

The formation of endoxifen is thought to be of most importance for the activity of tamoxifen treatment. An altered metabolism may contribute to the inter-individual variability in plasma concentrations of the active components (i.e. endoxifen), which in turn, possibly may affect treatment response to tamoxifen.

To create a better treatment outcome, it is probably neccesary to increase endoxifen concentrations. However, it is yet unclear whether endoxifen plasma concentrations will increase as result of a higher dose of tamoxifen. In case of impaired metabolism, due to inactive CYP2D6 enzymes for example, doubling of

the tamoxifen dose will probably not lead to double endoxifen concentrations. Furthermore, low endoxifen concentrations have also been observed in patients using 40 mg tamoxifen. Not only the supply of substrate, but also enzyme activity may be a rate limiting step for the metabolism of tamoxifen. Theoretically, induction of the metabolism of tamoxifen would be another option to achieve increased endoxifen levels.

Dextromethorphan was used as a putative phenotyping probe for tamoxifen pharmacokinetics in a previous study. This phenotyping probe appeared to be a better predictor of endoxifen exposure compared to CYP2D6 genotyping (predicting values of the variability in tamoxifen pharmacokinetics are 52% and 23% respectively). This *phenotyping* strategy has to be validated.

Amendment:
Results of the interim-analysis showed that co-administration of rifampicin resulted in strongly reduced plasma concentrations of tamoxifen as well as its metabolites. Therefore, we decided to stop rifampicin co-administration in the study. However, already informed patients can still participate in the study for pharmacokinetic analysis, without the use of rifampicin. Patients will be hospitalized once (during a 24-hour period) for pharmacokinetic blood sampling. Only dextromethorphan will be administered to the patients (secondary study objective).

Study objective

- To examine the effects of cytochrome P450 induction by rifampicin on the metabolism and pharmacokinetics of tamoxifen and its metabolites.

Induction of cytochrome P450 enzyme expression (including CYP3A4, CYP2C and CYP2D6) by rifampicin will probably lead to an increased metabolism of tamoxifen into its (active) metabolites, including endoxifen.The main goal of this study is to see whether it is possible to induce the metabolism of tamoxifen into endoxifen, irrespective of CYP2D6 genotype/phenotype. If it appears that endoxifen concentrations are significant higher after induction, there is a possibility created to increase endoxifen concentrations in future patients. Higher endoxifen concentrations in these patients may possibly lead to improved efficacy of tamoxifen therapy, which have to be evaluated in future studies.

- To validate the previously developed dextromethorphan phenotyping test.

Amendment:
Only secondary study objective: - Validation of the previously developed

dextromethorphan phenotyping test.

Study design

Amendment:
Already informed patients will be hospitalized during 24-hour for pharmacokinetic blood sampling (13 in total). Dextromethorphan will be administrated to the patients during both hospitalisation periods of the study for the validation of this *phenotyping* strategy.
Blood samples for genotyping will also be collected once during or before the study period (MEC 02.1002 protocol).

Intervention

Amendment:
- Dextromethorphan (30 mg, -base) administration.

Study burden and risks

Amendement:
Adverse effects of dextromethorphan administration may occur. However, the risk of adverse effects is expected to be minimal and adverse effects are of minor severity.

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

• Histological or cytological confirmed diagnosis of (invasive) breast cancer, for which treatment with tamoxifen monotherapy is indicated (to be evaluated by the treating physician);
• Use of tamoxifen monotherapy for at least 4 weeks (to guarantee steady-state) and willing to continue the treatment until the end of the study;
• Age >18 years;
• WHO performance <1;
• Adequate renal and hepatic functions (serum creatinin < 1.25x upper limit of normal (ULN), total bilirubin < 1.25xULN; alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) < 2.5x ULN, in case of liver metastasis < 5 ULN; alkaline phosphatase (AF) < 5xULN);
• Adequate hematological blood counts (absolute neutrophil count (ANC) > 1.5 x 109/L, platelets > 100 x 1012/L);
• Written informed consent;
• No chemotherapy within the last 4 weeks before start;
• No radiotherapy within the last 4 weeks before start;
• No concurrent (over the counter) medication or (herbal) supplements known to induce or inhibit CYP2D6, CYP2C, CYP3A4 and/or P-glycoprotein;
• Abstain from grapefruit, grapefruit juice, herbal dietary supplements, and herbal tea during the study.

Exclusion criteria

• Pregnant or lactating patients;
• Impossibility to take oral drugs;
• Serious illness or medical unstable condition requiring treatment, symptomatic CNS-metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;
• Contra-indications for dextromethorphan use;
• Use of medications or dietary supplements known to induce or inhibit CYP2D6, CYP2C, CYP3A4 and/or P-glycoprotein;
• Unwillingness to abstain from grapefruit (juice), (herbal) dietary supplements, herbals,

over-the-counter medication (except for paracetamol and ibuprofen) and other drugs known to seriously interact with CYP3A during the study period;
• Non-compliance

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):	03-03-2011
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Dextromethorphan (VICKS)
Generic name:	Dextromethorphan
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:	18-01-2011

Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-03-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2012
Application type:	Amendment
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	EUCTR2010-023776-52-NL
CCMO	NL34606.078.10