Phase I interaction study of Docetaxel and Tolbutamide with supplementation of Milk Thistle

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Primary objective: To determine pharmacokinetic interactions between milk thistle and docetaxel and between milk thistle and tolbutamide in patients with cancer.Secundary objective: To determine the safety of the use of milk thistle in combination...

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

Summary

ID

NL-OMON39305

Source
ToetsingOnline

Brief title
Interaction study of Docetaxel + Tolbutamide and Milk Thistle

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
cancer, malignant tumors

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: KWF Kankerbestrijding

Intervention

Keyword: Docetaxel, Interaction, Milk thistle, Tolbutamide

Outcome measures

Primary outcome

The most important parameter is the plasma concentration of docetaxel and tolbutamide and the course of this concentration with time in the presence or absence of milk thistle.

Secondary outcome

Secondary parameters are toxicities that patients experience from docetaxel in the presence or absence of milk thistle.

Study description

Background summary

The use of complementary and alternative medicines (CAM) by cancer patients has increased during the last years and we hypothesize that interactions between CAM and anticancer drugs can explain unexpected clinical toxicities and undertreatment of chemotherapy in cancer patients.

A CAM which is often used by cancer patients is milk thistle. Milk thistle is used as a self-treatment for hepatitis, cirrhosis, mushroom poisoning and for protection of the liver against toxicity of alcohol, acetaminophen and other hepatotoxic drugs. Milk thistle is also investigated for its potential anticancer effects.

In vitro assays, performed in our laboratory at Utrecht University, have shown that milk thistle inhibits the activity of hepatic enzymes CYP2C9 and CYP3A4. Thus, concomitant use of milk thistle could lead to significant interactions with (anticancer) drugs metabolized by these enzymes. In fact, CYP2C9 and CYP3A4 are involved in the metabolism of many anticancer drugs. However, there are no anticancer drugs which are solely metabolized by CYP2C9. This explains our choice for the well-studied CYP2C9 probe drug tolbutamide to assess the influence of milk thistle on CYP2C9 activity. The clinical effect of milk thistle on tolbutamide pharmacokinetics could also be of importance for

anticancer drugs that are partly metabolized by CYP2C9 and for concomitant medication that is metabolized by this enzyme.
Docetaxel, which is mainly metabolized by CYP3A4, has been chosen to investigate the effect of milk thistle on CYP3A4 activity. Inhibition of CYP2C9 and CYP3A4 by milk thistle is expected to increase plasma levels of tolbutamide and docetaxel.

Until now, no studies have been performed to examine the pharmacokinetics of docetaxel and tolbutamide with co-administration of milk thistle. To investigate whether the inhibition of CYP2C9 and CYP3A4 by milk thistle demonstrated in vitro, is of clinical importance, it is essential to perform this pharmacokinetic interaction study.

Study objective

Primary objective:
To determine pharmacokinetic interactions between milk thistle and docetaxel and between milk thistle and tolbutamide in patients with cancer.

Secundary objective:
To determine the safety of the use of milk thistle in combination with docetaxel or tolbutamide;
To establish guidelines to prevent unwanted interactions between complementary, alternative medicines (e.g. St. John*s wort, echinacea, milk thistle) and anticancer drugs in patients.

Study design

This is a phase I, randomized, crossover, open-label interaction study.

Included patients will be randomized in cohort A or cohort B.

Cohort A:
Day 0 of cycle 1 starts in the morning with oral administration of the officially registered milk thistle capsules in a dose of 1 capsule three times daily. This dosage regimen will be continued for 4 days (until day 3).
At approximately 09.00 h on day 1 patients will receive a subtherapeutic dose of 250 mg tolbutamide orally. Thereafter, at around 10.00 h, docetaxel will be administered intravenously for 120 min. as an absolute dose of 135 mg. The dose of 135 mg is based on a safe dose of 75 mg/m2 and a mean BSA of 1.8 m2. Pharmacokinetics of docetaxel and tolbutamide will be monitored until 48 h (day 3) after the start of administration of docetaxel. Further, on day 1 one blood sample will be drawn for CYP2C9 genotyping.

Day 3 will be followed by a wash out period from day 4 until day 21.
On day 1 of cycle 2, docetaxel (135 mg, IV) and tolbutamide (250 mg, PO) will

be administered for the second time under the same conditions as in cycle 1.

Cohort B:
Cycle 1 starts on day 1 at approximately 09.00 h with oral administration of 250 mg tolbutamide. At approximately 10.00 h docetaxel will be administered intravenously for 120 min. as an absolute dose of 135 mg. The dose of 135 mg is based on a safe dose of 75 mg/m2 and a mean BSA of 1.8 m2. Pharmacokinetics of docetaxel and tolbutamide will be monitored until 48 h (day 3) after the start of administration of docetaxel. Further, on day 1 one blood sample will be drawn for CYP2C9 genotyping.

In the morning of day 0 of cycle 2 patients in this cohort start with oral administration of the officially registered milk thistle capsules in a dose of 1 capsule three times daily. This dosage regimen will be continued for 4 days (until day 3 of cycle 2).
On day 1 of cycle 2, docetaxel (135 mg, IV) and tolbutamide (250 mg, PO) will be administered under the same conditions as in cycle 1.

Collected blood samples will be stored not longer than the duration of the study. After the end of the study, the blood samples will be destroyed.

Intervention

- Administration of 135 mg docetaxel and 250 mg tolbutamide on day 1 of cycle 1 and 2.
- Administration of 3 times daily 1 milk thistle capsule for 4 days.
- 2 times 24 h-hospital admission with bloodsampling for pharmacokinetics (including 1 blood sample for CYP2C9 genotyping).
- 6 times hospital visit for physical examination and bloodsampling for safety and/or pharmacokinetics.

Study burden and risks

- Administration of 135 mg docetaxel and 250 mg tolbutamide on day 1 of cycle 1 and 2.
- Administration of 3 times daily 1 milk thistle capsule for 4 days.
- 2 times 24 h-hospital admission with bloodsampling for pharmacokinetics (including 1 blood sample for CYP2C9 genotyping).
- 6 times hospital visit for physical examination and bloodsampling for safety and/or pharmacokinetics.

Toxiciteities of docetaxel will also be experienced by patients when they do not participate in the study and receive standard docetaxel therapy. No toxicities of milk thistle and a subtherapeutic dose of 250 mg tolbutamide are to be expected. There is a small risk of bruising by blood sampling.

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. Patients for whom treatment with docetaxel is considered to be of therapeutic benefit, e.g. advanced breast, gastric, esophagus, bladder, ovarian cancer and non-small cell lung cancer, head and neck cancer and prostate cancer
2. Histological or cytological proof of cancer
3. Age >= 18 years
4. WHO performance status of 0, 1 or 2
5. Patient is able and willing to give written informed consent
6. Patient is able and willing to swallow and retain oral medication
7. Patient is able and willing to undergo blood sampling for pharmacokinetics
8. Patient is willing to comply to the protocol and to follow dietary restrictions
9. Life expectancy > 3 months allowing adequate follow up of toxicity evaluation and antitumor activity

10. Minimal acceptable safety laboratory values
a. ANC of >= 1.5 x 10^9 /L
b. Platelet count of >= 100 x 10^9 /L
c. Hepatic function as defined by serum bilirubin <= 1.5 x ULN, ALAT and ASAT <= 2.5 x ULN
d. Renal function as defined by serum creatinine <= 1.5 x ULN or creatinine clearance >= 50 ml/min (by Cockcroft-Gault formula).
11. No radio- or chemotherapy within the last 4 weeks prior to study entry, except for pain palliation.

Exclusion criteria

1. Any treatment with investigation drugs within 30 days before the start of the study
2. Women who are pregnant or breast feeding
3. Concomitant use of MDR, CYP2C9 and CYP3A modulating drugs, food or drinks such as amiodaron, fluconazole, ketoconazole, clarithromycin, rifampicin, Ca2+-entry blockers (verapamil, dihydropyridines), cyclosporine, quinidine, quinine, tamoxifen, megestrol, grapefruit juice, concomitant use of HIV medications; other protease inhibitors, (non) nucleoside analogs, or St. John*s wort;
4.Unreliable contraceptive methods. Both men and women enrolled in this trial must agree to use a reliable contraceptive method throughout the study (adequate contraceptive methods are: condom, contraceptive pill (female partner), abstinence from sexual intercourse, sterilisation of man or woman).
5. Legal incapacity
6. Type I and II diabetes mellitus patients
7. Chronic use of H2-receptor antagonists or proton pump inhibitors
8. Unresolved (>grade 1) toxicities of previous chemotherapy
9. Bowel obstruction or motility disorders that may influence the absorption of drugs
10. Neurologic disease that may render a patient at increased risk for peripheral or central neurotoxicity
11. Symptomatic cerebral or leptomeningeal metastases
12. Uncontrolled infectious disease or known HIV-1 or HIV-2 type patients
13. Use of herbal supplements, especially milk thistle, within 6 weeks prior to study treatment.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	05-03-2012
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Orinase
Generic name:	Tolbutamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	29-10-2010
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	22-02-2011
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	28-04-2011
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO

Date:	20-03-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2013
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 27803
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2010-023415-34-NL
CCMO	NL34285.031.10
OMON	NL-OMON27803