Mass balance of docetaxel after administration of Oral Docetaxel in combination with Ritonavir

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON35601

Source
ToetsingOnline

Brief title
N11ODR

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancy

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Nederlands Kanker Instituut - Antoni van

Leeuwenhoek Ziekenhuis

Intervention

Keyword: Docetaxel, Mass balance, Oral, Ritonavir

Outcome measures

Primary outcome

The primary objective of this study is to quantitatively determine the pharmacokinetics (absorption, distribution, metabolism and excretion) of docetaxel (as ModraDoc003 10mg tablets) after administration of a single dose of oral docetaxel in combination with ritonavir.

Secondary outcome

- To determine the presence or absence of quantitatively relevant metabolites of docetaxel.

- To elucidate the structures of potential new metabolites of docetaxel

- To preliminary assess anti-tumor activity of oral docetaxel combined with ritonavir.

- To further characterize the safety and tolerability of oral docetaxel in combination with ritonavir.

Study description

Background summary

Oral administration has many advantages above intravenously administrated drugs for patients. However, oral bioavailability of docetaxel IV-solution is frequently low and variable. The bioavailability of docetaxel is limited due to metabolising cytochrome P450 (CYP) enzymes, which are abundantly present in the gastrointestinal tract. Inhibition of CYP3A4 enzymes with ritonavir (an anti-retroviral drug) has proven to enhance the bioavailability of oral

docetaxel in several trials.

The department of pharmacy of the Slotervaart Hospital and Netherlands Cancer Institute has developed several solid oral dosage forms for docetaxel, including ModraDoc001 (10 mg capsules) and ModraDoc003 (10 mg tablets). The ModraDoc001 (10 mg capsules) have been used in more than 90 patients in a Phase I clinical trial.

The metabolism of docetaxel, after oral administration in combination with ritonavir has not been investigated, nor has the route of elimination been determined. A mass balance study can provide essential knowledge on the absorption, metabolism and excretion of the drug.

Study objective

The primary objective of this study is to quantitatively determine the pharmacokinetics (absorption, distribution, metabolism and excretion) of docetaxel (as ModraDoc003 10mg tablets) after administration of a single dose of oral docetaxel in combination with ritonavir.

Study design

In this study patients will receive a single dose of 60 mg oral docetaxel (as ModraDoc003 10 mg tablets) and 200 mg ritonavir. This will be followed by collection of pharmacokinetic samples and excreta (urine and faeces). This is the mass balance part of the study. The samples of the first patient will be used as a proof of principle. The aim is to recover >80% of the administered docetaxel in the collected excreta. The 2nd patient will only enter the trial after analysis of the samples from the first patient and after evaluation of the results. Based on the recovery of docetaxel-derived products in the excreta of the first patient, a decision will be made either to continue with the sample collection and analysis procedures in the same way or to increase/decrease the collection period for excreta and/or to expand the bioanalytical assays for quantification of metabolites with additional metabolite(s).
In the subsequent or so-called extension phase of this study, which starts on day 15, patients continue with weekly docetaxel (60 mg) and ritonavir (200 mg) until progressive disease or until adverse events, which require dose modification or discontinuation of therapy, are observed.

Study burden and risks

- Patients participating will be hospitalized for 3 to 8 days, during which all urine and feces will be collected. Patients who collect their excreta on an out-patient basis (in consultation with principal investigator possible after at least 72h) will have to return to the hospital daily, up to day 8 for

collection of blood and delivery of urine and fecal samples. Thereafter, collection of excreta is continued on an out-patient basis until day 15 or less, depending on the recovery-time profile of docetaxel-related products of the first patient.
- Blood will be drawn for pharmacokinetic research, hematology, and serum chemistry.
- After the first cycle, all patients will have to visit the hospital on a weekly basis. After the first tumor evaluation (6-8 weeks after start treatment), this is changed to every two weeks.
- Patients are at risk for docetaxel related side effects.

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. Histological or cytological proof of cancer
2. Patient for whom no standard therapy of proven benefit exist
3. Patients who might benefit from treatment with docetaxel, e.g. advanced breast, gastric, esophagus, bladder, ovarian cancer and non-small cell lung cancer, head and neck cancer, prostate cancer and carcinoma of unknown primary site.
4. Age GE 18 years
5. Able and willing to give written informed consent
6. Able and willing to undergo blood sampling for pharmacokinetics
7. Able and willing to comply with the study protocol for the duration of the study
8. Life expectancy GE 3 months allowing adequate follow up of toxicity evaluation and antitumor activity
9. Minimal acceptable safety laboratory values
a. ANC of GE 1.5 x 10^9 /L
b. Platelet count of GE 100 x 10^9 /L
c. Hepatic function as defined by serum bilirubin LE 1.5 x ULN, ALAT and ASAT LE 2.5 x ULN
d. Renal function as defined by serum creatinine LE 1.5 x ULN or creatinine clearance GE 50 ml/min (by Cockcroft-Gault formula).
10. WHO performance status of 0, 1 or 2
11. No radio- or chemotherapy within the last 4 weeks prior to study entry (except for palliative single dose radiotherapy for pain reduction)
12. Able and willing to swallow oral medication;GE = Greater or Equal than
LE = Less or Equal than

Exclusion criteria

1. Patients with known alcoholism, drug addiction and/or psychotic disorders in the history that are not suitable for adequate follow up
2. Women who are pregnant or breast feeding.
3. 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, sterilization, other barrier contraceptive measures preferably in combination with condoms).
4. Concomitant use of MDR and CYP3A modulating drugs such as Ca+ -entry blockers (verapamil, dihydropyridines), cyclosporine, quinidine, quinine, tamoxifen, megestrol and grapefruit juice, concomitant use of HIV medications; other protease inhibitors, (non) nucleoside analoga, St. Johns wort or macrolide antibiotics as erythromycin and clarithromycin.
5. Uncontrolled infectious disease or known HIV-1 or HIV-2 type patients
6. Unresolved (>grade 1) toxicities of previous chemotherapy
7. Bowel obstructions or motility disorders that may influence the absorption of drugs
8. Chronic use of H2-receptor antagonists or proton pump inhibitors
9. Neurologic disease that may render a patient at increased risk for peripheral or central

neurotoxicity
10. Pre-existing neuropathy greater than CTC grade 1
11. Symptomatic cerebral or leptomeningeal metastases
12. Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
13. Legal incapacity

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2011
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Docetaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritonavir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-10-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-12-2011
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2011-004263-77-NL
CCMO	NL38034.031.11