Weekly administration of Oral Docetaxel in combination with Ritonavir

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To determine the maximum tolerated dose (MTD), dose limiting toxicities (DLT), and optimal dose of docetaxel that can safely be administered to patients with cancer in a weekly schedule. amendment 1The objective of the first amendment is to...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Observational invasive

Summary

ID

NL-OMON39153

Source
ToetsingOnline

Brief title
N07DOW

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
advanced cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: docetaxel, Oral, paclitaxel, ritonavir, weekly

Outcome measures

Primary outcome

To determine the maximum tolerated dose (MTD), dose limiting toxicities (DLT), and optimal dose for oral docetaxel/ritonavir that can safely be administered to patients with cancer as monotherapy in a weekly schedule.

Secondary outcome

To determine the hematologic and non-hematologic toxicity.

To preliminary assess anti-tumor activity of docetaxel and paclitaxel

To determine the PK of oral docetaxel and paclitaxel

To establish the effect of functional genetic polymorphisms in genes encoding for Pgp, MRP2, OATP1B3, CYP3A4, CYP3A5 and CYP2C8

To determine the effect of the timing and dose of RTV on the PK of docetaxel.

To determine the systemic exposure of the new capsule formulation of docetaxel, with or without coating, in combination with ritonavir.

To investigate whether the systemic exposure to docetaxel can also be enhanced by other CYP3A4 inhibitors, especially ketoconazole, grapefruit juice and claritromycin.

To preliminary investigate whether the systemic exposure to paclitaxel can also be enhanced by CYP3A4 inhibitors; ritonavir, ketoconazole, or claritromycin

To preliminary determine the systemic exposure of the new oral pacltiaxel formulation with or without an eneric coating in combination with ritonavir

Study description

Background summary

Oral administration has many advantages above intravenously administrated drugs for patients. However, oral bioavailability is frequently low and variable. The bioavailability of docetaxel and paclitaxel are limited due to metabolising cytochrome P450 (CYP) enzymes and p-glycoprotein (a transporter enzyme), which are abundantly present in the gastrointestinal tract. Inhibition of CYP3A4 enzymes with ritonavir, (an anti-retroviral drug) has in a previously conducted proof-of-concept trial, shown to enhance the bioavailability of oral docetaxel and possibly also from paclitaxel.

Study objective

To determine the maximum tolerated dose (MTD), dose limiting toxicities (DLT), and optimal dose of docetaxel that can safely be administered to patients with cancer in a weekly schedule.

amendment 1
The objective of the first amendment is to determine the effect of a second ritonavir dose 4 hours post-dose on the pharmacokinetics of docetaxel.

amendment 2
THe objective of the second amendment is to determine the systemic exposure of the new oral docetaxel formulation (ModraDoc001 capsules) in combination with ritonavir.

amendment 3
The results of Arm C justify to continue the development of an oral docetaxel/rionavir regimen with ModraDoc001 capsules instead of the liquid formulation. therefore we would like to continue in Arm A and B with the capsule formulation, ModraDoc001 capsules. therefore we would like to continue in doselevel 2 of Arm A, the dose escalating part of the study, with the capsule formulation instead of the liquid formulation. Patients treated in Arm B receive in each course 30 mg ModraDoc001 capsules.

Amendment 4:
Is it necessary to administer the novel oral formulation of docetaxel, ModraDoc001 capsules, with a booster to enhance the systemic exposure?
-Are there other, frequently used CYP3A4 inhibitors (ketoconazole, Grapefruit juice) that also increase the systemic exposure of oral docetaxel (ModraDoc001 capsules)?
-Has ritonavir a similar effect on the apparent bioavailability of paclitaxel?
These questions will be addressed in Arm D, E and F.

Amendment 5:
-Can claritromycin, a macrolide antibacterial agent and strong CYP3A inhibitor, enhance the systemic exposure to docetaxel and paclitaxel after oral administration?
-Can ketoconazole enhance the systemic exposure to oral paclitaxel?
These questions relate to the extent of the concept of boosting docetaxel and paclitaxel by inhibition of CYP3A.

The formulation of oral paclitaxel currently used has a few disadvantages. Due to its main excipients, alcohol and cremophor, it has a bad taste and it also has a limited shelf life. The department of pharmacy of the Slotervaart hospital and Netherlands Cancer Institute developed an improved formulation. This new formulation, ModraPac001 capsules, will be investigated in part C to see whether this new formulation has comparable pharmacokinetic characteristics to the orally administered iv formulation.

Amendment 6:
In arm K, the influence of a double ritonavir dose (200 mg) will be investigated. The combination of oral docetaxel in combination with ritonavir has been investigated thoroughly. However, to assess the optimal ritonavir dose, the impact of higher ritonavir doses needs to be assessed.
An important issue to address is whether the final formulation for both docetaxel and paclitaxel should be coated with an enteric protective coat. The influence of an enteric coat on the bioavailability is investigated. This concerns arms L and M of the protocol.

amendment 7:
in Arm A i.v. docetaxel is given on week 1. this is omitted in doselevel 5 and higher.

amendment 8:
doselevel 6 will be 60 mg ModraDoc001 in combination with 200 mg RTV.
addition of arm L: 100 or 200 mg RTV in combination with oral paclitaxel.
study arms with coated modraDoc001 capsules are removed from the protocol.

amendment 9:
addition of pharmacogenetic analysis

amendment 10:
switch from ritonavir capsules to ritonavir tablets.

amendment 11:
physical exam once every two weeks instead of weekly.

amendmet 13:
To determine the systemic exposure of the oral docetaxel formulation (ModraDoc005 tablets) in combination with ritonavir.

To determine dose limiting toxicities (DLT) and recommended dose (RD) of docetaxel (ModraDoc005 tablets) that can safely be administered to patients with cancer in a weekly schedule.

amendment14:
To determine the systemic exposure of the oral docetaxel formulation (ModraDoc006 tablets) in combination with ritonavir.
To determine dose limiting toxicities (DLT) and recommended dose (RD) of docetaxel (ModraDoc006 tablets) that can safely be administered to patients with cancer in a weekly schedule.

Study design

Arm A
The optimal dose of docetaxel in combination with ritonavir will be determined by dose escalation. Three patients are assigned to each dose level.
On day 1 of the first week, each patient receives docetaxel 20 mg iv and ritonavir 100 mg.
On the first day of the second and every subsequent week, the patient receives ritonavir and oral docetaxel, dosed according to the dose escalation schedule. This regime will be continued weekly until progressive disease or until adverse events, which require dose modifications or discontinuation of therapy, are observed. In doselevel 2 patients receive 40 mg ModraDoc001 capsules instead of the liquid formulation.
In doselevel 5 and higher, patients will not receive iv docetaxel. Patients immediately start with oral docetaxel. PK samples will be drawn during the first and second week.

Arm B:
The patients are randomized into two groups. The first group receives:
* Cycle 1, Day1: 20 mg docetaxel in combination with 100 mg RTV
* Cycle 2, Day 1: 20 mg docetaxel in combination with 100 mg RTV and 100 mg RTV 4 hours post-dose.
Each cycle lasts 7 days.
Cycle 1 and 2 are reversed for the second randomization group.
Patients continue in cycle 3 with 30 mg docetaxel in combination with 100 mg RTV in a weekly schedule until progressive disease or adverse events, which require dose modifications or discontinuation of therapy, are observed. This dose is the starting dose of the dose escalating trial, arm A.
The first two patients were treated according to the above schedule, patiented treated after approval of amendment 3 will be treated in each course with 30 mg ModraDoc001 capsules.

Arm C:
A new oral formulation of docetaxel will be investigated in part C. The patients are randomized into two groups. The first group receives:
* Cycle 1, Day 1: 30 mg docetaxel in combination with 100 mg RTV

* Cycle 2, Day 1: 30 mg ModraDoc001 capsules in combination with 100 mg RTV.
* Cycle 3, Day 1: 30 mg ModraDoc001 capsules in combination with 100 mg RTV.
Each cycle lasts 7 days.
Cycle 1 and 3 are reversed for the second randomization group.
Patients continue in cycle 4 with 30 mg docetaxel (i.v. formulation) in combination with 100 mg RTV in a weekly schedule until progressive disease or adverse events, which require dose modifications or discontinuation of therapy, are observed. This dose is the starting dose of the dose escalating trial, arm A.

Arm D, E and Arm G:
Different CYP3A4 modulating agents are investigated in these arms:
* Cycle 1, Day 1: 30 mg ModraDoc001 capsules
* Cycle 2, Day 1: 30 mg ModraDoc001 capsules in combination with 100 mg ritonavir
* Cycle 3, Day 1: 30 mg ModraDoc001 capsules in combination with 400 mg ketoconazole
Each cycle lasts 7 days.
Cycle 2 and 3 are reversed for the second randomization group.

in Arm E: patients are treated with 2 glasses of grapefruit juice instead of ketoconazole (simultaneously and 1 hour after ModraDoc001 capsulesintake).

Arm G: patients do not receive ModraDoc001 capsules without booster (due to poor results of ModraDoc001 capsules alone, when administered without booster). Patients reveive 1000 mg claritromycine instead of 400 mg ketoconazole

Patients continue in cycle 4 or cycle 3 (arm G) with 30 mg docetaxel (ModraDoc001 capsules) in combination with 100 mg RTV in a weekly schedule until progressive disease or adverse events, which require dose modifications or discontinuation of therapy, are observed.

Arm K:
In total, 4 patienten will be randomzied into 2 groups. group1 will recieve the schedule depicted below. Cycle 1 and 2 are reveresed for the second randomization group.
Cycle1 day 1: 30 mg ModraDoc001 capsules and 100 mg ritonavir
Cycle2 day 1: 30 mg ModraDoc001 capsules and 200 mg ritonavir

Arm L:
In total, 4 patienten will be randomzied into 2 groups. group1 will recieve the schedule depicted below, the second group receives first the second cycle and subsequently the first cours.
Cycle1 day 1: 30 mg ModraDoc001 capsules and 100 mg ritonavir
Cycle2 day 1: 30 mg ModraDoc002 capsules and 100 mg ritonavir

Patients assigned to arm K or L continue in cycle 3 with 40 mg docetaxel

(ModraDoc001 capsules) in combination with 100 mg RTV in a weekly schedule until progressive disease or adverse events, which require dose modifications or discontinuation of therapy, are observed.

Arm F, H and I:
Different CYP3A4 modulating agents are investigated in these arms, arm F:
* Cycle 1, Day 1: 100 mg paclitaxel po in combination with 15mg/kg cyclosporin A po
* Cycle 2, Day 1: 100 mg paclitaxel in combination with 100 mg ritonavir
Each cycle lasts 7 days.
Cycle 1 and 2 are reversed for the second randomization group.

In arm H and I patients follow the same schedule as for arm F. Except, instead of cyclosporin A, patients recveive 1000 mg claritromycine in arm H and 400 mg ketoconazole in arm I.

Arm M: Has not been opened for patients, no patients have been recruited, in amendment 13 a new arm M has been introduced
In total, 4 patienten will be randomzied into 2 groups. group1 will recieve the schedule depicted below, the second group receives first the second cycle and subsequently the first cours.
Cycle1 day 1: 30 mg Modrapac001 and 100 mg ritonavir
Cycle2 day 1: 30 mg Modrapac002 and 100 mg ritonavir

In Arm F, H, I, J and M: Patients continue in cycle 3 with a weekly 1-hour infusion schedule of 90 mg/m2 paclitaxel until progressive disease or adverse events, which require dose modifications or discontinuation of therapy, are observed.

Arm M: after amendment 13
Dose escalation cohor with ModraDoc005, 3-13 patient per dose level, with a maximum of 18 patients in this arm M.

Arm N: introduced in amendment 14
Dose escalation cohor with ModraDoc006, 3-13 patient per dose level, with a maximum of 18 patients in this arm N.

Study burden and risks

The safety profile for oral administrated docetaxel is expected to be similar as intravenously administered docetaxel. Gastrointestinal side effects might occur more frequently due to the oral route of administration.
Twenty-five patients treated in a phase II trial with weekly oral docetaxel 100 mg and cyclosporine 15 mg/m2 were evaluable for respons and toxicity. The main

toxicities were: neutropenia, diarrhea, nail toxicity and fatigue.

Ritonavir has been administered to healthy volunteers at oral doses of 600 mg at 12 hour intervals. Vomiting, nausea and abdominal pain occur frequently especially during the first few weeks of therapy but only at the highest doses. These ritonavir side effects correlate with ritonavir plasma levels. Thus, the expected burden andf risks associated with ritonavir are low.

Side effects from cyclosporin and ketoconazole are not expected. both drugs are administrated only once, while sideeffects generally are observed when administered on a continues base.
Possible side effects from claritromycine are diarrhea and vomitting.
Overall, the risks associated with the study procedures are low. For most people, needle punctures for blood samples do not cause any serious problems. However, this procedure may cause bleeding, bruising, discomfort, infections and or pain at the needle site.

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. Patients 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 cancers, prostate cancer and carcinoma of unknown primary site. ;4. Age > 18 years;5. Able and willing to give written informed consent;6. Able and willing to undergo blood sampling for pharmacokinetics;7. Life expectancy > 3 months allowing adequate follow up of toxicity evaluation and anti-tumor activity;8. Minimal acceptable safety laboratory values;a. ANC of > 1.5 x 109 /L;b. Platelet count of > 100 x 109 /L;c. Hepd. Renal function as defined by serum creatinine < 1.5 x ULN or creatinine clearance > 50 ml/min (by Cockcroft-Gault formula).;9. WHO performance status of </= 2;10. No radio- or chemotherapy within the last 4 weeks prior to study entry (palliative limited radiation for pain reduction is allowed);11. Able and willing to swallow oral medication;atic function as defined by serum bilirubin < 1.5 x ULN, ALAT and ASAT < 2.5 x ULN;12. Arm F: Patients for whom weekly paclitaxel can seriously be considered therapy with palliative intent, with tumortypes that reasonably will respond.

Exclusion criteria

1. Patients with known alcoholism, drug addiction and/or a history of psychotic disorders that are not suitable for adequate follow up;2. Women who are pregnant or breast feeding. ;3. Both men and women who do not agree to use a reliable contraceptive method throughout the study ;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, or St. Johns wort.;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 resorption of drugs;9. Neurologic disease that may render a patient at increased risk for peripheral or central neurotoxicity;10. Symptomatic cerebral or leptomeningeal metastases;11. Acid neutralizing medicines (e.g. aluminium hydroxide), should not be administered for at least 2 hours prior to and after the intake of ketoconazol (Arm D)

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-12-2007
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Neoral
Generic name:	cyclosporin A
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Nizoral
Generic name:	ketoconazole
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Norvir
Generic name:	ritonavir
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
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:	13-09-2007
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-10-2007
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-06-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-06-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-10-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-11-2008
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-03-2009

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-12-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-04-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-06-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-12-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-01-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-02-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-04-2012
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Approved WMO Date:	01-11-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-03-2017
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-03-2017
Application type:	Amendment
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	EUCTR2007-004520-20-NL
ISRCTN	ISRCTN32770468
CCMO	NL19276.031.07