Weekly administration of (bi-)daily Oral Docetaxel in combination with Ritonavir

Published: 15-03-2010
Last updated: 04-05-2024

The primary objective is to determine the maximum tolerated dose (MTD) of docetaxel (as ModraDoc001) that can safely be administered to patients with cancer in a bi-daily weekly schedule.

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-OMON39193

Source
ToetsingOnline

Brief title
N10BOM

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, oral, ritonavir

Outcome measures

Primary outcome

• To determine the maximum tolerated dose (MTD) of docetaxel (as ModraDoc001 10 mg capsules) that can safely be administered in combination with ritonavir to patients with cancer in a bi-daily weekly schedule.

Secondary outcome

• To determine the systemic exposure of the bi-daily ModraDoc001 10 mg capsules in combination with ritonavir.

• To determine the hematological and non-hematological toxicity profile of oral docetaxel in combination with ritonavir.

• To preliminary assess anti-tumor activity of docetaxel.

• To determine the systemic exposure of the novel oral docetaxel formulation (ModraDoc003 10 mg tablets) in combination with ritonavir.

• To determine the systemic exposure of the novel oral docetaxel-ritonavir co-formulation (ModraDoc004 10/50 mg tablets).

• To determine the effect of co-formulating docetaxel with ritonavir on the systemic exposure of docetaxel.

• To determine the inter- and intrapatient variability in plasma pharmacokinetics of docetaxel and ritonavir of ModraDoc001 10 mg capsules in combination with ritonavir, ModraDoc003 10 mg tablets in combination with ritonavir and ModraDoc004 10/50 mg tablets.

• To establish the effect of functional genetic polymorphisms in five genes

(SLCO1B3, ABCB1, ABCC2, CYP3A4 and CYP3A5) on the pharmacokinetics of oral docetaxel and ritonavir.

• 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 bi-daily weekly schedule.

• 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 bi-daily weekly schedule.

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 HospitalSlotervaart Hospital Slotervaart Hospital and Netherlands Cancer Institute developed a solid oral dosage form for docetaxel, ModraDoc001 10 mg capsules. This formulation has now been investigated in more than 40 patients in a first clinical study. Currently, a dose escalation study of weekly administration (once daily) of oral docetaxel (as ModraDoc001 10 mg capsules) in combination with ritonavir is in progress at the NKI. The preliminary results of this study are promising and a linearity between systemic exposure to docetaxel and the applied dose of

ModraDoc001 10 mg capsules is seen. In an attempt to further improve and prolong the systemic exposure we will explore a twice daily dosing schedule. This assessment will be done in arm A of this study with a classical dose escalation design, starting with the highest daily administration which is proven tolerable in the comparable dose escalation study (i.e. 40 mg BID).

The department of pharmacy developed recently two other novel dosage forms for docetaxel, ModraDoc003 10 mg tablets and ModraDoc004 10/50 mg tablets. Both are spray dried solid dispersions of docetaxel pressed in tablets. The distinction between both is that ritonavir is included in the co-formulation of ModraDoc004 10/50 mg tablets. Both dosage forms will be investigated in arm B to see whether these new formulations have comparable pharmacokinetic characteristics of docetaxel to the capsule formulation.

Oral administration of docetaxel has proven to be feasible in arm A. The MTD is determined as 20 mg docetaxel as ModraDoc001 capsules in combination with 100 mg ritonavir BID. However, the production process of the capsule formulation is labor intensive and therefore not suitable for possible phase II trials. Based on the results of arm B, which has showed no significant differences in exposure between ModraDoc001 10 mg capsules and ModraDoc003 10 mg tablets, the department of pharmacy of the Slotervaart hospital developed an improved tablet formulation. This new formulation, ModraDoc005 tablets, will be investigated in an additional dose finding cohort (arm C) to determine the toxicity profile and the pharmacokinetics.
ModraDoc006 tablets, will be investigated in an additional dose finding cohort (arm D) to determine the toxicity profile and the pharmacokinetics. This arm is added because of dissapointing bioavailability of the ModraDoc005 tablets.

Study objective

The primary objective is to determine the maximum tolerated dose (MTD) of docetaxel (as ModraDoc001) that can safely be administered to patients with cancer in a bi-daily weekly schedule.

Study design

Arm A:
The optimal dose of bi-daily docetaxel in combination with ritonavir will be determined with a classical dose escalation design. On a predefined day of the first and every subsequent week, the patient will receive oral docetaxel (as ModraDoc001 10 mg capsules), dosed according to the escalation schedule (see *Dose escalation*) and ritonavir. This regime will be continued weekly (intake around the same time) until progressive disease or until adverse events, which require dose modification or discontinuation of therapy, are observed.
Three patients will be assigned to each dose level. If one patient of the first three at a defined dose level experiences dose limiting toxicity (DLT), the

number of patients treated at this dose level will be expanded to a maximum of six. The dose escalation will continue if none of the additional patients experiences a DLT. The MTD level will be expanded to at least six patients.

The first dose level was not tolerable for two of the five patients. Although only one of the two patients had a formal DLT, the dose level of 40 mg docetaxel BID was not proven to be safe and tolerable. Therefore the next dose level will be 20 mg docetaxel BID (equals 40 mg per week). If this dose level is proven safe and tolerable, dose escalation will proceed to 30 mg docetaxel BID. The dose of ritonavir will remain 100 mg BID (equals 200 mg on one day/week).

Arm B:
Both new oral dosage forms, ModraDoc003 10 mg tablets and ModraDoc004 10/50 mg tablets, will be investigated to see whether these new formulations have comparable pharmacokinetic characteristics of docetaxel when given as ModraDoc001 10 mg capsules. Six evaluable patients will be randomized in a way that all possible treatment regimes are given. The patients will receive 40 mg docetaxel (as ModraDoc001 10 mg capsules, ModraDoc003 10 mg tablets and ModraDoc004 10/50 mg tablets) and 200 mg ritonavir once daily (a week). Patients continue in Week 4 with 80 mg ModraDoc001 10 mg capsules in combination with 100 mg ritonavir once daily in a weekly schedule until progressive disease or adverse events, which require dose modifications or discontinuation of therapy, are observed. Patients should take the ModraDoc001 10 mg capsules, ModraDoc003 10 mg tablets and ModraDoc004 10/50 mg tablets in the morning on an empty stomach (This means at least 2 hours of fasting before intake of ModraDoc and after intake at least 1 hour before a breakfast can be taken). ModraDoc001 10 mg capsules and ModraDoc003 10 mg tablets will be administered simultaneously with 200 mg ritonavir. The docetaxel dose during the first three weeks will be 40 mg.

Arm C:
The design of this part of the study is comparable with arm A. ModraDoc005 tablets will be investigated to determine the toxicity profile and the pharmacokinetics. The starting dose will be 20mg docetaxel and 100 mg ritonavir BID (dose level 2 of arm A), since this dose was the maximum tolerated dose with capsules in arm A. Docetaxel and ritonavir are administered on a predefined day of each week. This schedule will be continued weekly until it is no longer in the patient*s best benefit. The dose level will start with three patients. If none of the patients has experienced a DLT, a new dose level may be started according to the percentages of the escalation rules of arm A. If one patient has experienced a DLT, the dose level will be expanded to six patients. If still less than two patients (out of six) have experienced a DLT, a new dose level may be started according to the percentages of the escalation rules of arm A. If two patients have experienced a DLT, a new dose level will be started with a lower dose of docetaxel (to be determined by the principal investigator after careful evaluation of safety and PK of the actual dose

level). Every dose level can be expanded to six patients, if less than 2 DLTs have occurred. The final recommended dose for future phase II will be expanded to a maximum of twelve patients.

Arm D:
The design of this part of the study is comparable with arm A. ModraDoc006 tablets will be investigated to determine the toxicity profile and the pharmacokinetics. This arm was added because of low bio-availability of the ModraDoc005 tablets. The starting dose will be 20 mg docetaxel and 100 mg ritonavir BID (dose level 2 of arm A), since this dose was the maximum tolerated dose with capsules in arm A. Docetaxel and ritonavir are administered on a predefined day of each week. This schedule will be continued weekly until it is no longer in the patient*s best benefit. The dose level will start with three patients. If none of the patients has experienced a DLT, a new dose level may be started according to the percentages of the escalation rules of arm A. If one patient has experienced a DLT, the dose level will be expanded to six patients. If still less than two patients (out of six) have experienced a DLT, a new dose level may be started according to the percentages of the escalation rules of arm A. If two patients have experienced a DLT, a new dose level will be started with a lower dose of docetaxel (to be determined by the principal investigator after careful evaluation of safety and PK of the actual dose level). Every dose level can be expanded to six patients, if less than 2 DLTs have occurred. The final recommended dose for future phase II will be expanded to a maximum of twelve patients.

Study burden and risks

- Patients participating will be hospitalized during the first and fifteenth day and night. (Arm B: first, eighth and fifteenth day)
- Blood will be drawn for pharmacokinetic research, hematology, and serum chemistry (see *Pharmacokinetics*).
- All patients will have to visit the hospital once every week and on day 3 and 17. After the first tumor evaluation, patient-visits will be once every two weeks.
- Patients are at risk for docetaxel related side effects. Currently, a comparable dose escalation study of weekly administration (once daily) of oral ModraDoc001 in combination with ritonavir is ongoing at the NKI. Hitherto, the highest dose which is proven tolerable, is 80 mg. According to preliminary results the AUC is comparable with historical data of weekly IV administration (35 mg/m2), but no severe (grade 3-4) hematologic adverse events have been seen yet in the dose escalation.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL

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. 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).;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

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. 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 excluding alopecia;7. Bowel obstructions or motility disorders that may influence the absorption of drugs;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.

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:	Recruitment stopped
Start date (anticipated):	04-04-2010
Enrollment:	48
Type:	Actual

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:	15-03-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-04-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-08-2010
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:	14-03-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-03-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-11-2011
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
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	01-11-2013

Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-09-2014
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	EUCTR2010-019166-91-NL
ClinicalTrials.gov	NCT01173913
CCMO	NL31787.031.10