Phenotyping study of the CYP3A4 activity in patients with prostate cancer versus male patients with other types of solid tumours with midazolam

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The primary objective is comparison of the CYP3A4 activity in medically castrated patients with prostate cancer with the CYP3A4 activity of male patients with other types of solid tumours. To evaluate the CYP3A4 activity, the PK of the CYP3A4…

Ethical review	Approved WMO
Status	Completed
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON51249

Source
ToetsingOnline

Brief title
Phenotyping of CYP3A4 activity with Midazolam

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
prostate cancer and other types of solid tumours

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: NKI-AVL

Intervention

Keyword: CYP3A4 activity, midazolam, other solid tumours, prostate cancer

Outcome measures

Primary outcome

To compare the CYP3A4 activity in prostate cancer patients versus patients with other types of solid tumours, by use of a midazolam phenotyping test

Secondary outcome

- To measure plasma concentrations of midazolam

- To determine metabolite pharmacokinetics of midazolam

- Since polymorphisms in genes encoding for CYP3A4 can be important determinants in the pharmacokinetics of midazolam, single nucleotide polymorphisms in these genes will be assessed retrospectively

- exploratory: to differentiate between hepatic and gastro-intestinal CYP3A4 activity by comparison of oral and intravenous midazolam PK

Study description

Background summary

The metabolizing enzyme cytochrome P450 (CYP) 3A4 is an important factor in the pharmacokinetics (PK) of many (anticancer) drugs, including taxanes. Recently, it has been reported that the PK of intravenous docetaxel are different in patients with castration resistant prostate cancer, as compared to patients with other types of solid tumours. Different phase I studies with the oral docetaxel formulation ModraDoc006 in combination with ritonavir (denoted as ModraDoc006/r), were conducted in our institute in patients with

hormone-sensitive prostate cancer, castration-resistant prostate cancer (CRPC) and other types of solid tumours. The exposure to docetaxel and ritonavir after administration of the same dose and schedule of ModraDoc006/r was substantial lower in prostate cancer patients as compared to the patients with other types of solid tumours.
The underlying mechanism for these observations remains to be elucidated. The lower docetaxel exposure with IV and oral docetaxel treatment and the lower ritonavir exposure with ModraDoc006/r treatment might be related to a higher CYP3A4 activity in prostate cancer patients. Therefore, it is important to directly compare the CYP3A4 activity with a phenotyping test in prostate cancer patients and patients with other types of solid tumours.
As a potential cause for this, CYP3A4 activity might be altered by medical castration. Franke et al. showed that the clearance of docetaxel was higher in castrated versus non-castrated prostate cancer patients. However, comparison of the CYP3A4 activity in the castrated versus the prostate cancer patients with normal levels of testosterone showed no significant differences. However, this was done in 6 CRPC patients, of which one patient had an extremely low CYP3A4 activity. The intravenous erytromycin breath test that was used in this study only reflects the hepatic CYP3A4 activity and not the gastro-intestinal CYP3A4 activity. The latter is important in treatment with oral docetaxel (ModraDoc006) in combination with ritonavir. Furthermore, erythromycin is also a substrate for P-gp indicating that the erythromycin breath test might reflect P-gp activity as well as CYP3A4 activity. Therefore, it is necessary to evaluate prostate cancer patients with a phenotyping test that includes both the hepatic and gastro-intestinal CYP3A4-activity.
Midazolam is one of the most frequently used test compounds used for evaluation of CYP3A4 activity. Midazolam has several advantages over other CYP3A4 probes such as erythromycin, dapsone, quinine, and nifedipine. First, midazolam is selectively metabolized by CYP3A4. Furthermore, midazolam clearance after both oral and intravenous administration is a widely accepted and validated metric of CYP3A4 activity. Continuing, midazolam AUC and metabolite clearance to its major metabolite 1-hydroxy midazolam correlate well with hepatic CYP3A content. Also, midazolam PK are highly sensitive to changes in CYP3A4 activity. Therefore, oral midazolam will be used in this study to further evaluate the CYP3A4 activity in prostate cancer patients in comparison to patients with other types of solid tumours. Both oral and intravenous midazolam will be used to be able to differentiate between the gastro-intestinal and the hepatic CYP3A4 activity.

Study objective

The primary objective is comparison of the CYP3A4 activity in medically castrated patients with prostate cancer with the CYP3A4 activity of male patients with other types of solid tumours. To evaluate the CYP3A4 activity, the PK of the CYP3A4 substrate midazolam will be investigated after oral and intravenous administration.

Study design

On day 1, oral midazolam (2 mg) will be administered, followed by PK sampling until 8 hours postdose
On day 2, intravenous midazolam (1 mg) will be administered, followed by PK sampling until 8 hours postdose

Intervention

On day 1, oral midazolam (2 mg) will be administered, followed by PK sampling until 8 hours postdose
On day 2, intravenous midazolam (1 mg) will be administered, followed by PK sampling until 8 hours postdose

Study burden and risks

Participation is based on motivation to help with scientific research and has no personal benefit for patients. The burden consist of hospitalization time of 2 days (staying overnight is not obligated), insertion of a venous peripheral infusion needle for pharmacokinetic sampling, and administration of oral and intravenous midazolam. Complications of the venous infusion needle are flebitis, bruising and bleeding. Possible side effects of midazolam are sedation and drowsiness.

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. Male patients receiving anticancer treatment or supportive care within our institute
• Group 1: histological or cytological proof of prostate cancer, for which the treatment leads to castrate levels of testosterone, defined as <= 50 ng/dL (or <= 0.50 ng/mL or 1.73 nmol/L)
• Group 2: histological or cytological proof of cancer.
2. Considered fit for midazolam treatment as assessed by the treating physician.
3. Age >= 18 years.
4. Able and willing to give written informed consent.
5. Able and willing to undergo blood sampling for PK and pharmacogenetic analysis.
6. Able and willing to comply with study restrictions and to remain at the study center for the required duration.
7. Adequate bone marrow, hepatic and renal functions

Exclusion criteria

1. Concomitant use of medication, herbs or food which could influence the pharmacokinetics of midazolam within 14 days or five half-lives of the drug (whichever is shorter) before start of the study, consisting of (but not limited to) CYP3A4-inhibitors/inducers. In particularly, use of enzalutamide, bicalutamide and dexamethasone is not allowed within 14 days before start of the study. The use of prednisolone is allowed at a maximum daily dose of 10 mg.

2. Current smokers or patients who stopped smoking within 7 days before study allocation

3. Cachexia as evaluated by a modified Glasgow Prognostic Score (mGPS) of 2: albumin <35 g/L and CRP >= 10 mg/L

4. Patients with a known psychological or physical condition and/or expected

poor prognosis, which in the opinion of the investigator, contra-indicates hospitalization and/or participation in the study for the individual patient.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	22-04-2021
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	02-02-2021
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
CCMO	NL75583.031.20

Study results

Date completed: 02-12-2022

Results posted: 15-04-2024

First publication
01-01-1900