Effects of dosing time on the pharmacokinetics and pharmacodynamics of sunitinib.

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Primairy objective:To investigate whether the pharmacokinetics of sunitinib are influenced by circadian rhythm.Secondary objective:- to investigate whether daily variation in CYP3A4 activity exists in humans, based on midazolam and 4beta-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39190

Source
ToetsingOnline

Brief title
Effects of dosing time of sunitinib on its drug levels

Condition

- Other condition
- Renal and urinary tract neoplasms malignant and unspecified

Synonym
GIST, p-NET, renal cell carcinoma

Health condition

GIST, p-NET

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: chronopharmacology, pharmacodynamics, pharmacokinetics, sunitinib

Outcome measures

Primary outcome

Pharmacokinetic values: AUC and clearance

Secondary outcome

Toxicity (hypertension, fatigue, diarrhea, skin toxicity, mucositis, nausea,

anorexia, any grade 3-4 toxicity).

Difference in CYP3A4 activity in the morning and evening

Study description

Background summary

Since metabolism of sunitinib is dependant of different cytochrome P450 enzymes, including CYP3A4, which in cell-lines and rodents show a circadian rhythm in expression, it is very likely that pharmacokinetics of sunitinib is time dependant. The activity of CYP3A4 probably drops in night time. Higher concentrations of sunitinib and its active metabolite may be reached when sunitinibin the evening or afternoon.
This study is highly relevant, as sunitinib is a frequently used tyrosine kinase inhibitor, without a clear advise on the intake times for this drug. Higher levels of sunitinib and its active metabolite may result in better anticancer effect. In a previous study, there was no increase in adverse events when sunitinib was administered in the evening [17]. Therefore, it is safe to administrate sunitinib in the evening, and potentially achieve a better anticancer effect. We will compare the (plasma) pharmacokinetics of sunitinib and its active metabolite N-desethyl-sunitinib at steady state when taken in the morning to the pharmacokinetics when taken in the afternoon or evening. In addition, we will closely monitor the side-effects (pharmacodynamics) during all treatment cycles.

To investigate the circadian rhythm of CYP3A4, patients will be administered a low dose of midazolam. Pharmacokinetics of midazolam and 1OH-midazolam will be measured. In addition, also the endogenous marker 4beta-hydroxycholesterol will be studied as an extra test to study CYP3A4 dynamics.

Study objective

Primairy objective:
To investigate whether the pharmacokinetics of sunitinib are influenced by circadian rhythm.

Secondary objective:
- to investigate whether daily variation in CYP3A4 activity exists in humans, based on midazolam and 4beta-hydroxycholesterol PK.
- to investigate if evening dosing of sunitinib affects the side effects of this drug.
- to investigate the influence of single-nucleotide polymorphisms in PK genes on the exposure to sunitinib (based on the MEC02.1002 protocol).

Study design

This is a single center cross-over pharmacokinetic study intended to investigate a circadian rhythm in sunitinib pharmacokinetics. The study will be performed at the Erasmus MC, Daniel den Hoed Cancer Center. It is anticipated that the study will be completed within 24 months. A total of 18 evaluable patients will be treated with sunitinib at standard dosing of 50 mg once daily, in a 4 weeks on, 2 weeks off scheme or a 37.5 mg continuous daily dose. Patients will be deemed evaluable if blood withdrawal for pharmacokinetics is completed at steady state in 1. one course when sunitinib is taken in the morning and 2. in another course when sunitinib is taken in the evening. After registration (see section 9), patients will be randomized to start in arm A (50%) or arm B (50%). Patients in study arm A will start in the first course after enrollment with sunitinib in morning dosing at 8.00 AM (+/- 1 hour), and the second course in evening dosing at 06.00 PM (+/- 1 hour). Arm B will start in the first course after enrollment with sunitinib in the evening at 06.00 PM (+/- 1 hour), and the second course in the morning at 08.00 AM (+/-1 hour). After switching from morning to evening dosing or vice versa, patients must use sunitinib at this time point for at least 2 weeks. During the third course patient will take sunitinib at 1 PM.
After completing these three courses, patients are free to decide at wich time they will continue sunitinib intake.

Intervention

Afternoon and evening intake of sunitinib in stead of morning intake of

sunitinib.

Study burden and risks

The burden for patients that participate in this study is low. Patients will be hospitalized three times for 24 hours for PK sampling. PK samples will be taken from an intravenous canule, so that patients don't need intravenous puncture for every sample.
At one of the hospitalisations the PK samples will take place during the day.
At the other hospitalisation day, samples will be drawn in the evening and once during the night. (For further information on sampling times, see protocol Table 3)
The risk of participation in this study are low. Hematomas can occur when removing the canule.
In a previous study, there was no increase in toxicity when sunitinib was administered in the evening compared to the morning dose.

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

Age >= 18 years;;Histological or cytological confirmed diagnosis of advanced clear-cell renal cell carcinoma, GIST or pancreatic neuro-endocrine tumor, treated with sunitinib;;WHO performance score <= 1 at study entry (see appendix A of the protocol);;Any stable dose of sunitinib at study entry, defined as no dose change within 3 weeks prior to pharmacokinetics; ;Adequate hematological functions (ANC > 1.0 x 109/L, platelets > 100 x 1012/L);;Adequate liver and renal function defined as bilirubin concentration <= 2 x ULN, AST and ALT <= 2.5 x ULN, serum creatinin concentration <= 2 x ULN;;Written informed consent;;For patients with reproductive potential a reliable method of contraception (excluding oral contraceptives) must be used

Exclusion criteria

Pregnant or child nursing patients;;Serious illness or medical unstable condition requiring treatment, symptomatic CNS metastasis or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;;Major surgery within 2 weeks prior to start of the protocol;;Use of CYP3A4 inhibiting or inducing medication as listed in appendix C;;Patients who are unable to collect blood from;;Patients with known allergy to sunitinib or midazolam;;Patients unwilling or unable to give written informed consent

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-07-2012

Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Sutent
Generic name:	Sunitinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-03-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-07-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-03-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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: 20106
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2012-000425-45-NL
CCMO	NL39931.078.12
OMON	NL-OMON20106