Use of individual PK-guided sunitinib dosing: A feasibility study in patients with advanced solid tumors

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Primary: • To determine the safety and feasibility of PK guided dosing of sunitinib
Secondary:• To determine the objective response rate (according RECIST 1.1)• To determine the time to tumor progression and progression free survival• To validate...

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

Summary

ID

NL-OMON34224

Source
ToetsingOnline

Brief title
PK-guided dosing of sunitinib

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancies

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Pfizer,Pfizer inc.

Intervention

Keyword: dried blood spots, pharmacokinetics, sunitinib, therapeutic drug monitoring

Outcome measures

Primary outcome

Tumor response (RECIST): ORR, PR, TTP, PFS

Toxicity (CTC v4.2)

Secondary outcome

Pharmacokinetics (dried blood spots): total trough levels

Pharmacogenetics: polymorfism of genes involved in pharmacokinetic and

pharmacodynamic pathways.

Study description

Background summary

In a large percentage of patients on sunitinib treatment (30 - 50%), dose reductions are required because of multiple grade 2 toxicities or due to grade 3 or 4 toxicities. Therefore, the currently used dosing schedule is not optimal.
Recently, a dose-efficacy relation was established for sunitinib treatment. This large meta-analysis of pharmacokinetic/pharmacodynamic data from studies performed in mRCC patients, GIST patients and patients with solid tumors, clearly showed a relationship between sunitinib exposure and efficacy and tolerability. Both time to progression (TTP) and overall survival (OS) were significantly better for mRCC patients with high area under the curve (AUC) compared to low AUC. This was not only observed for sunitinib exposure but also for its active metabolite SU12662. In addition, there was a significant relationship between exposure and probability of partial response (PR) or complete response (CR) in mRCC patients (p=0.00001), indicating that a dose intensity in patients should be as high as possible.
Since this is a retrospective (meta-) analysis from patients treated in several studies, we propose to perform a prospective feasibility study in 30 patients with PK guided dosing of sunitinib. The number of patients with advanced renal cell carcinoma is limited and since the safety of sunitinib treatment is independent of tumour type, we decided to perform this feasibility study in a

normal phase I population consisting of patients with any advanced cancer for whom no standard treatment options are available and who are in good clinical condition. This will also shorten the time period to a randomized controlled trial (RCT).
If PK guided once-daily continuous sunitinib dosing is feasible, a RCT in mRCC patients will be performed comparing PK guided dosing with a standard sunitinib dosing schedule.

Study objective

Primary:
• To determine the safety and feasibility of PK guided dosing of sunitinib

Secondary:
• To determine the objective response rate (according RECIST 1.1)
• To determine the time to tumor progression and progression free survival
• To validate previously identified associations between genetic markers in the pharmacokinetic and pharmacodynamic pathways of sunitinib and the development of toxicities.

Study design

A prospective feasibilty study of patients with solid tumors on a sunitinib dosing schedule of 37.5 mg continous daily dosing.
On two fixed timepoints during the study there is a possibility to adjust the dose of sunitinib based on total trough levels of the drug and its metabolite in PK samples (dried blood spots) and a predefined dose modification scheme.
At t=8 weeks a third trough level measurement will be performed and patients will be evaluated by CT- or MRI-scans for the response to therapy.
Treatment will be continued until progressive disease or until adverse events, which require discontinuation of therapy, are observed.

Intervention

Patients will start receiving once daily oral sunitinib, dosed according to the standard dosing schedule of 37.5 mg continuous daily dosing.
On two fixed timepoints during the study there is a possibility to adjust the dose of sunitinib based on total trough levels of the drug and its metabolite in PK samples (dried blood spots) and a predefined dose modification scheme.

Study burden and risks

The burden for the patient exists of weekly physical examinations, blood hematology and blood chemistry parameters during the first 8 weeks, and monthly thereafter. These assessments will guide the safety of the treatment. In addition, the patient is asked to perform a finger prick at home three times

during the first 8 weeks of the study for pharmacokinetic assessments. In short, this will give a minimal additional burden for patients compared to treatment with regular patient care.
The possible benefit for patients within this study is the optimisation of the dose which probably can lead to prevention of toxicities and treatment failure. Therefore, we think that the possible benefits of this study can compensate for the minimal burden associated with participation in this study.

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. Patients with histopathologically confirmed advanced or metastatic solid tumors for whom sunitinib is standard therapy, of for whom no standard therapy is available;2. Age >= 18 years;;3. Able and willing to give written informed consent;;4. Able and willing to undergo

blood sampling for pharmacogenetic and pharmacokinetic analysis;;5. Able to swallow oral medications;6. Life expectancy >= 3 months, allowing adequate follow up of toxicity evaluation and antitumor activity;;7. WHO performance status of 0 or 1;;8. Evaluable disease according to RECIST 1.1 criteria;;9. Minimal acceptable safety laboratory values
• ANC of >= 1.5 x 109 /L
• Platelet count of >= 100 x 109 /L
• Hepatic function as defined by serum bilirubin <= 1.5 x ULN, ASAT and ALAT <=
• 2.5 x ULN
• Renal function as defined by serum creatinine <= 1.5 x ULN or creatinine clearance >= 50 mL/min (by Cockcroft-Gault formula);;10. No radio- or chemotherapy or other investigational drug treatment within the last 4 weeks prior to study entry, with the exception of palliative radiotherapy (8Gy, or in the extremities).

Exclusion criteria

1. Current treatment in another therapeutic clinical trial;2. Congestive heart failure, myocardial infarction or coronary artery bypass graft in the previous six months, ongoing severe or unstable angina or any unstable arrhythmia requiring medication;3. Patients with known alcoholism, drug addiction and/or psychotic disorders in the history that are not suitable for adequate follow up;4. Women who are pregnant or breast feeding.;5. Both men and women enrolled in this trial must agree to use a reliable contraceptive method throughout the study (definition of adequate contraceptive methods will be based on the judgment of the principal investigator or a designated associate). ;6. Legal incapacity.;7. Known allergy/intolerance to sunitinib or any of the excipients.

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):	11-04-2011
Enrollment:	30

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:	02-09-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-12-2010
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-01-2011
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-03-2011
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	EUCTR2010-021454-20-NL
CCMO	NL32967.031.10