Therapeutic Drug Monitoring to Individualize the Dosing of pazopanib: a Randomized Pharmacokinetic Feasibility Study

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Primary objectiveTo evaluate the effect of PK-guided individualized dosing of pazopanib on the interindividual variability in drug exposure.Secondary objective- To determine the correlation between pazopanib trough and exposure levels - To determine…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive and genitourinary neoplasms gender unspecified NEC
Study type	Interventional

Summary

ID

NL-OMON37356

Source
ToetsingOnline

Brief title
TIP-study

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC

Synonym
advanced tumors for which no treatment options are available, renal cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Farmaceutische Industrie (glaxosmithkline)

Intervention

Keyword: Advanced Solid Tumor, NONMEM, Pazopanib

Outcome measures

Primary outcome

By introducing PK-guided dosing we hypothesize that the interpatient variability can be reduced by 50%. In this relatively small feasibility study we collect the evidence that PK-guided dosing in the future can be applied to increase efficacy and reduce toxicity by targeting the right exposure levels of pazopanib.

Secondary outcome

1. A correlation of at least 80% between pazopanib trough and exposure levels is required to make the translation of pazopanib trough levels to pazopanib exposure legitimate for future clinical application.

Hypothesis:

The correlation between pazopanib trough levels and exposure levels are > 80%.

Sample size:

To address this hypothesis the required 13 patient for the primary endpoint are sufficient (10 patients are required) as was tested with a bivariate correlations the Pearson test, and P <.05 was regarded as statistically significant Pearson correlation.

2. Explore, quantify and describe the accuracy of the pazopanib exposure of the PK-guided vs. fixed dose regimen (geometric mean ratio should be 1 * 0.2).

3. Explore, quantify and describe the effect of pazopanib exposure on the

change in systolic and diastolic blood pressure compared to baseline

measurements.

4. Explore quantify and describe the effect of dose individualization on the

frequency of the scored adverse events (CTCAE v4.0).

- Explore, quantify and describe the feasibility of measuring pazopanib

concentrations with the dried blood spot sampling technique.

Study description

Background summary

In the recent years, nine tyrosine kinase inhibitors (TKIs) and two m-TOR inhibitors have been approved for cancer treatment and numerous are under investigation. These targeted anticancer therapies are generally considered to be less toxic than conventional chemotherapy since they specifically inhibit cellular processes that are deregulated in various types of tumor cells. However, dose interruptions or reductions appears to be necessary in a large number (20 * 50%) of patients treated with these drugs. Additionally, recent publications indicate that efficacy might be related to TKI exposure. Since TKIs and m-TOR inhibitors show a large interpatient variability (35 * 60%) the fixed dose administered will result in very different exposure levels between individuals resulting in supratherapeutic or subtherapeutic exposure levels and consequently in over- or undertreatment. Dose individualization based on the measured drug concentration could theoretically result in less toxicity and more efficacy. However before the effect of dose individualization on the clinical outcome can be studied the effect of pharmacokinetic guided individualization on the interpatient variability should first be studied. Since, if we are incapable of inducing a more predictable and stable drug exposure (reduced interpatient variability) by introduction of PK guidance * titration of the drug based on PK guidance will never lead to the predefined exposure level / trough level.

Study objective

Primary objective
To evaluate the effect of PK-guided individualized dosing of pazopanib on the interindividual variability in drug exposure.

Secondary objective

- To determine the correlation between pazopanib trough and exposure levels
- To determine the accuracy of the exposure levels (e.g. the deviation between the mean AUC at fixed dose and after dose adjustment) after the introduction of PK guided dosing
- To determine the effect of pazopanib exposure on the systolic and diastolic blood pressure
- To determine the effect of dose individualization on the frequency of the scored adverse events (CTCAE v4.0)
- To investigate the feasibility and accuracy of quantifying pazopanib concentrations with dried blood spot sampling.

Study design

The study is a randomized, multicenter, open label, cross-over design phase I study.
Patients are initially randomized to either the fixed dose treatment arm or the PK-guided treatment arm. The target exposure (AUC) of 805 *g*hr/mL is derived from the mean exposure level measured in 29 patient treated with a single dose of pazopanib 800 mg (AUC0-t after a single dose is equal to AUC0-24 at steady-state)1. All patients will start with the standard dose:
- once daily 800 mg pazopanib, 1hr before or 2hr after food consumption
At day 14, blood samples are collected at 0, 1, 2, 3, 4, 6, 8, 10 and 24 hours after pazopanib from patients in both treatment arms and measured within 3 business days by LC-MS/MS. In the PK-guided treatment part the therapy will be continued with an adjusted dose based on the deviation between the target (805 *g*hr/mL) and measured exposure (table I)1. Patients in the fixed dose treatment arm will continue with the same dose as started with.
Fourteen days after the dose adjustment the exposure to the drug will be measured again in both treatment arms.
At day 28, the second PK-observation day, patients will switch between the treatment arms. The dose of the patients in the fixed arm will be adjusted based on the deviation between the target and measured exposure. The patients in the PK-guided arm will return to the standard dose.
At the third PK-observation day, day 42, the exposure to the drug will be measured in both treatment arms (figure I).

The pazopanib plasma concentration will be measured within 3 business days after the last sample collected by LC-MS/MS. The treating physician will call the patient to communicate the adjusted dose and explain details regarding the adjusted dose (e.g. number of tablets, possible side effects that require earlier contact).

Systolic and diastolic blood pressure will be measured at four different time points over a time frame of three hours at baseline and at day 7, 14, 28 and 42 after initiating pazopanib therapy.

All patients will return to the standard treatment intensity and will remain on

treatment until they do no longer have clinical benefit from treatment, progressive disease according to RECIST V1.1 or if adverse events lead to patient withdrawal.

Patients with an elevated dose who develop adverse events and theoretically require a dose reduction according to the section *Dose Modification Algorithms for Potential Treatment-Related Adverse Events* will be evaluated for earlier PK assessment (measurement of AUC0-24hr) after which they can return to the standard dose of 800 mg pazopanib OD. If earlier PK assessment is not legitimate they will be withdrawn from the study and replaced by a new eligible patient.
All other patient who develop adverse events and theoretically require a dose reduction according to the section *Dose Modification Algorithms for Potential Treatment-Related Adverse Events* will be evaluated for earlier PK assessment; thereafter they will be withdrawn from the study and replaced by a new eligible patient.

Intervention

PK guided dose adjustments based on a dosing algorithm

Study burden and risks

Patients are admitted to the hospital for 3 days in a six week period
Blood sampels are withdrawn - total of 27 sampels of 5mL

Benefit
Patients are treated with a active compound that might result in tumor response

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
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- No radio-, chemo- or tumorspecific targeted therapy within the last 4 weeks prior to study entry
- Adequate organ system function
- Patients or partners of patients with childbearing potential should practice adequate contraception (double barrier protection).
- Patient who are lactating should discontinue nursing prior to the first dose and should refrain from nursing throughout the treatment period and for 14 days following the last dose of study drug.

Exclusion criteria

- Current treatment in another therapeutic clinical trial
- History or clinical evidence of central nervous system (CNS) metastases or leptomeningeal carcinomatosis, except for individuals who have previously-treated CNS metastases, are asymptomatic, and have had no requirement for steroids or anti-seizure medication for 6 months prior to first dose of study drug.
- Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding
- Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product
- Presence of uncontrolled infection.
- Corrected QT interval (QTc) > 480 msecs using Bazett*s formula (QTc = QT/*RR)
- History of any one or more of the following cardiovascular conditions within the past 6 months:
* Cardiac angioplasty or stenting

* Myocardial infarction
* Unstable angina
* Coronary artery bypass graft surgery
* Symptomatic peripheral vascular disease
- Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA)
- Poorly controlled hypertension [defined as systolic blood pressure (SBP) of *140 mmHg or diastolic blood pressure (DBP) of * 90mmHg].
- History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
- Prior major surgery or trauma within 28 days prior to first dose of study drug and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major).
- Evidence of active bleeding or bleeding diathesis.
- Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels
- Hemoptysis in excess of 2.5 mL (or one half teaspoon) in the last 8 weeks
- Increased risk of haemorrhage (treated with coumarines or low molecular weight heparine).
- Any serious and/or unstable pre-existing medical, psychiatric, or other condition that could interfere with subject*s safety, provision of informed consent, or compliance to study procedures.
- Unable or unwilling to discontinue use of prohibited medications listed in appendix B for at least 14 days or five half lives of a drugs (whichever is longer) prior to the first dose of study drug and for the duration of the study
- Concurrent use of other substances known or likely to interfere with the pharmacokinetics of pazopanib (http://medicine.iupui.edu/clinpharm/ddis/)
- Treatment with any of the following anti-cancer therapies:
a. radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR
b. chemotherapy, immunotherapy, biologic therapy, investigational therapy or hormonal therapy within 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of pazopanib
- Any ongoing toxicity from prior anti-cancer therapy that is >Grade 1 and/or that is progressing in severity, except alopecia.

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2012
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Votrient
Generic name:	pazopanib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	29-12-2011
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	14-02-2012
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	12-03-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	26-03-2012

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	03-04-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2011-006007-35-NL
CCMO	NL39091.058.11