Will pazopanib dose individualization result in less variability in pazopanib bloodconcentrations between individuals.

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON22313

Source
NTR

Brief title
TIP-study

Health condition

Cancer,
Solid tumor
Phase I

Sponsors and support

Primary sponsor: Leiden University Medical Center
Source(s) of monetary or material Support: GlaxoSmithKline

Intervention

Outcome measures

Primary outcome

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

Secondary outcome

1. To determine the correlation between pazopanib trough and exposure levels;

2. 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;

3. To determine the effect of pazopanib exposure on the systolic and diastolic blood pressure;

4. To determine the effect of dose individualization on the frequency of the scored adverse events (CTCAE v4.0).

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

By introducing of PK-guided individualized dosing of pazopanib we hypothesize that the interpatient variability can be reduced by 50%.

Study design

1. PK samples collected over 24 hours on day 14, 28 and 42 of treatment with pazopanib;

2. On day 7, 14, 28 and 42 the bloodpressure will be measured;

3. In week 8 response to treatment will be scored.

Intervention

Dose adjustment based on pazopanib blood concentrations.

Patients will be treated with pazopanib for 6 weeks. When effective they will continue use until progression or until intolerancy.

During 4 weeks the patients will receive 800 mg pd. The other 2 weeks they will receive an individualized dose.

These 2 weeks will either be received after 2 weeks of the standard dose or after 4 weeks.

Contacts

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Eligibility criteria

Inclusion criteria

1. Eligible patients for study entry include patients who have histologically or cytologically confirmed diagnoses of mRCC for which pazopanib is registered as the first line treatment OR

Patients with a cytological/histological diagnosis of an advanced solid tumor for whom pazopanib may be a valuable treatment option as judged by the treating physician;

2. Patients must provide written informed consent prior to performance of study-specific procedures or assessments, and must be willing to comply with treatment and follow up. Procedures conducted as part of the subject's routine clinical management (e.g., blood count, imaging study) and obtained prior to signing of informed consent may be utilized for screening or baseline purposes provided these procedures are conducted as specified in the protocol;

3. Age ≥ 18 years;

4. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2;

5. No radio-, chemo- or tumorspecific targeted therapy within the last 4 weeks prior to study entry;

6. Adequate organ system function;

7. Patients or partners of patients with childbearing potential should practice adequate contraception (double barrier protection);

8. 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

1. Current treatment in another therapeutic clinical trial;

2. 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;

3. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding;

4. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product;

5. Presence of uncontrolled infection;

6. Corrected QT interval (QTc) > 480 msecs using Bazett's formula (QTc = QT/RR);

7. History of any one or more of the following cardiovascular conditions within the past 6 months:

A. Cardiac angioplasty or stenting;

B. Myocardial infarction;

C. Unstable angina;

D. Coronary artery bypass graft surgery;

E. Symptomatic peripheral vascular disease.

8. Class III or IV congestive heart failure, as defined by the New York Heart Association (NYHA);

9. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of ≥140 mmHg or diastolic blood pressure (DBP) of ≥ 90mmHg];

10. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months;

11. 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);

12. Evidence of active bleeding or bleeding diathesis;

13. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels;

14. Hemoptysis in excess of 2.5 mL (or one half teaspoon) in the last 8 weeks;

15. Increased risk of haemorrhage (treated with coumarines or low molecular weight heparine);

16. 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;

17. 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;

18. Concurrent use of other substances known or likely to interfere with the pharmacokinetics of pazopanib (http://medicine.iupui.edu/clinpharm/ddis/);

19. 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.

20. 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
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2012
Enrollment:	13
Type:	Anticipated

Ethics review

Positive opinion

Date:	16-02-2012
Application type:	First submission

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
NTR-new	NL3149
NTR-old	NTR3293
Other	METC LUMC : P11.217
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Study results

Summary results
N/A