Use of individual PK-guided pazopanib 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 pazopanib secondary• Evaluation of the dried blood spot procedure• To determine the objective response rate (according RECIST 1.1)• To determine the time to tumor progression...

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

Summary

ID

NL-OMON40372

Source
ToetsingOnline

Brief title
PK-guided pazopanib dosing

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancy

Research involving
Human

Sponsors and support

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

Intervention

Keyword: individualized dosing, pazopanib, pharmacokinets, therapeutic drug monitoring

Outcome measures

Primary outcome

see objectives

Secondary outcome

see objectives

Study description

Background summary

Pazopanib has been reported to inhibit numerous tyrosine kinases, including VEGFR-1,2,3, PDGFR α/β, FGFR, c-Kit, Itk, Lck and c-Fms. Votrient (pazopanib hydrochloride; GlaxoSmithKline, UK), was approved by FDA in October, 2009 and EMA in June, 2010 for the treatment of RCC; it is also approved by FDA in April, 2012 and by EMA in August, 2012 for the treatment of STS. The recommended dose of pazopanib for the treatment of RCC or STS is a flat-fixed dose of 800 mg (maximum) once-daily.

In general most intravenous anti-cancer agents are dosed according to body surface area (BSA) or weight of the patient and most oral anti-cancer agents are used with a flat-fixed dose. All these methods are far from optimal since they do not take the inter- en intrapatient variability in pharmacokinetics (PK) into account. Due to the small therapeutic window of anti-cancer agents, this may lead to suboptimal doses in a substantial number of cancer patients treated. Especially with the oral anti-cancer drugs such as tyrosine kinase inhibitors (TKIs) variability in PK can be very high (due to the added PK variability resulting from differences in absorption between patients) thereby leading to ineffective treatment or unwanted toxicity when a fixed dose is used.

In multiple papers it has been discussed why TDM in treatment with oral anti-cancer drugs (like TKIs) could increase tumor response rates and progression free survival in cancer patients.

Target plasma concentrations of pazopanib are set at >=20.0 µg/mL. Optimal inhibition of tumor angiogenesis was observed in preclinical studies when plasma pazopanib concentrations of >=17.5 µg/mL (40 µmol/L) were maintained over

the entire dosing interval. Week 4 pazopanib Cmin > 20.6 µg/mL levels were associated with improved efficacy. This means that the threshold for efficacy for this drug will be near 20 µg/mL, although the exact number is hard to establish, and may even vary between patient-subgroups.
Maintaining a minimum threshold concentration is relevant for observing optimal benefit with pazopanib. Hurwitz et al demonstrated the interindividual variance in exposure, showing that flat-fixed dosing of 800 mg daily (the currently registered dose) results in inadequate trough levels in almost half of the patients. There seems to be a dose-exposure relationship suggesting that increasing the dose may result in more patients achieving adequate trough levels. However, the number of patients with doses above 800 mg/day are too limited to support this and prospective TDM studies have not been performed sofar.

The primary objective of this study is to assess the feasibility of using individual PK-guided pazopanib dosing in patients while controlling for unacceptable toxicity.

Study objective

primary
• To determine the safety and feasibility of PK guided dosing of pazopanib

secondary
• Evaluation of the dried blood spot procedure
• To determine the objective response rate (according RECIST 1.1)
• To determine the time to tumor progression and progression free survival

Study design

Patients with advanced tumors for which pazopanib is considered standard or patients with advanced or metastatic tumors for whom no standard therapy is available, and who are in good clinical condition will be eligible. Patients will start receiving once daily oral pazopanib, dosed according to the standard dosing schedule of 800 mg continuous daily dosing. One treatment cycle will be defined as a 28 days continuous dosing period.

Weekly in the first 8 weeks and every 4 weeks thereafter trough levels of pazopanib will be collected and measured by LC-MS/MS. During the entire treatment period, 3 moments of potential individual dose increments are defined; week 3 day 1 (W3D1 = D15); week 5 day 1 (W5D1 = D29) and week 7 day 1 (W7D1 = D43). The decision for dose increments are based on trough levels taken 1 week earlier to account for bioanalytical sample turn-around time of max. 7 days. Trough levels (TL) for pazopanib should be >=20.0 µg/mL. If the trough level is <15.0 µg/mL and the patient does not show any treatment related >=grade 2 toxicity, the daily pazopanib dose will be increased with 400 mg (2 dose

levels). If the trough level is <15.0 µg/mL and the patient does shows any treatment related grade 2 toxicity, the daily pazopanib dose will be increased with 200 mg (1 dose level). If the trough level is between 15.0 and 20.0 µg/mL and the patient does not show any treatment related >=grade 3 toxicity, the daily pazopanib dose will be increased with 200 mg (1 dose level). (see Tables 1 and 2) If the total trough level is <20.0 µg/mL, but the patient suffers from >= grade 3 toxicity, dose will be interrupted until the toxicity is the toxicity was treatment related the dose will be lowered with 200 mg or to
the previous dose in case of earlier dose increments. If the total trough level is >=20.0 µg/mL and the patient does not show toxicity > grade 1 or 2, the dose will be continued. If the trough level is >=20.0 µg/mL and the patient suffers from >=grade 3 toxicity the pazopanib dose will be interrupted until toxicity is 200 mg or to the previous dose in case of earlier dose increments. (Table 1 and 2).

During the course of the study no dose increments are allowed after a previous dose reduction for toxicity.

Weekly in the first 8 weeks and every 4 weeks thereafter trough level measurement will be performed. Patients will be evaluated by CT- or MRI-scans for the response to therapy at week 8, and thereafter every 8 weeks.

Treatment will be continued until progressive disease, until patient refusal or until adverse events, which require discontinuation of therapy, are observed. Weekly physical examination, blood hematology and blood chemistry parameters in the first 2 cycles, and monthly thereafter, will guide the safety of the treatment.

Table 1. Dose Levels

Dose Level Daily Dose (mg) Change from Level 1
-2 400 QD -400
-1 600 QD -200
0 800 QD 0
+1 1000 QD +200
+2 1200 QD +400
+3 1400 QD +600
+4 1600 QD +800
+5 1800 QD +1000
+6 2000 QD +1200

Patients who need major surgery should discontinue pazopanib 24 h before surgery and resume treatment at least two weeks after surgery.
Pazopanib dose will not be decreased to less than 400 mg daily and no further increased than 2000 mg daily.

Patients will start receiving once oral pazopanib, dosed according to the standard dosing schedule of 800 mg continuous daily dosing.
At day 8 ± 1day, a first trough level of pazopanib will be measured by LC-MS/MS. The outcome of the trough level measurement will be reported to the physician within maximally seven days after receipt of the samples. Trough levels should be >= 20.0 µg/mL. If the trough level is <15.0 µg/mL and the patient does not show any treatment related >=grade 2 toxicity, the daily pazopanib dose will be increased with 400 mg (2 dose levels). If the trough level is <15.0 µg/mL and the patient does show any treatment related grade 2 toxicity, the daily pazopanib dose will be increased with 200 mg (1 dose level). If the trough level is between 15.0 and 20.0 µg/mL and the patient does not show any treatment related >=grade 3 toxicity, the daily pazopanib dose will be increased with 200 mg (1 dose level). (see Tables 1 and 2) If the total trough level is <20.0 µg/mL, but the patient suffers from >= grade 3 toxicity, dose will be interrupted until the toxicity is treatment related the dose will be lowered with 200 mg or to the previous dose
in case of earlier dose increments. If the total trough level is >=20.0 µg/mL and the patient does not show toxicity > grade 1 or 2, the dose will be continued. If the trough level is >=20.0 µg/mL and the patient suffers from >=grade 3 toxicity the pazopanib dose will be interrupted until toxicity is 200 mg or to the previous dose in case of earlier dose increments. (Table 1 and 2, see chapter 8.4).

Seven days ± 1day after the first pazopanib dose adjustment (day 22 after start of treatment) the second trough level will be measured and dose adjustment will be performed as described above (Table 1). A final dose adjustment decision will be made at day 43 (based on the TL drawn at day 36).

Trough levels will be measured weekly in the first 8 weeks and every 4 weeks thereafter. During the entire treatment period, only 3 moments of potential individual dose increments are defined; week 3 day 1 (W3D1 = D15); week 5 day 1 (W5D1 = D29) and week 7 day 1 (W7D1 = D43).

Pazopanib dose will not be decreased to less than 400 mg once daily and no further increased than to 2000 mg once daily.

(see *Table 1 for dose levels and Table 2 for instructions for dose modifications*)
Patients will remain on treatment until they have no longer clinical benefit or disease progression, or if toxicity leads to patient withdrawal.

Intervention

see study design

Study burden and risks

The burden of blood sample drawings is limited.
Pazopanib is regisgtered for use and side effects of the drug are known. These are managable.

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) Subjects 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.
Note: Procedures conducted as part of the subject*s routine clinical management (e.g., blood count, imaging study such as bone scan) 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
2) Age >= 18 years
3) Histopathologically confirmed advanced tumors for which pazopanib is considered standard of care or patients with advanced or metastatic tumors for whom no standard therapy is available;
4) Eastern Cooperative Oncology Group (ECOG) or WHO performance status of 0-1
5) Evaluable disease according to RECIST 1.1 criteria
6) Adequate organ system function as defined in Table 3
Table 3: Definitions for Adequate Organ Function
System Laboratory Values
Hematology
Absolute neutrophil count (ANC) *1.5 X 109/L
Hemoglobina
*5.6 mmol/L
Platelets *100 X 109/L
Prothrombin time (PT) or international normalized ratio (INR)a *1.2 X ULN
Activated partial thromboplastin time (aPTT) *1.2 X ULN
Hepatic
Total bilirubin *1.5 X ULN
Alanine amino transferase (ALT) and Aspartate aminotransferase (AST)b *2.5 X ULN
Renal
Serum creatinine *133 µmol/L
Or, if >133 µmol/L : Calculated creatinine clearance (ClCR) *30 mL/min to *50 mL/min
Urine Protein (disptick) <2+
Or, 24-hour urine protein <1g
a. Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
b. Concomitant elevations in bilirubin and AST/ALT above 1.0 x ULN (upper limit of normal) are not permitted.;7) Women of childbearing potential must have a negative serum pregnancy test within 14 days of first dose of study treatment and agree to use effective contraception during the study and for 14 days following the last dose of investigational product.

Exclusion criteria

1. Central nervous system (CNS) metastases at baseline, with the exception of those subjects who have previously-treated CNS metastases (surgery ± radiotherapy, radiosurgery, or gamma knife) and who meet both of the following criteria: a) are asymptomatic and b) have no requirement for steroids or enzyme-inducing anticonvulsants in prior 4 week interval.
2. Clinically significant gastrointestinal abnormalities that may increase the risk for gastrointestinal bleeding
3. Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product
4. Corrected QT interval (QTc) > 480 msecs

5. 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)
6. Poorly controlled hypertension [defined as systolic blood pressure (SBP) of >=140 mmHg or diastolic blood pressure (DBP) of >= 90mmHg].
Note: Initiation or adjustment of antihypertensive medication(s) is permitted prior to study entry. Following antihypertensive medication initiation or adjustment, blood pressure (BP) must be re-assessed three times at approximately 2-minute intervals. At least 24 hours must have elapsed between anti-hypertensive medication initiation or adjustment and BP measurement. These three values should be averaged to obtain the mean diastolic blood pressure and the mean systolic blood pressure. The mean SBP / DBP ratio must be <140/90 mmHg (OR 150/90 mm Hg, if this criterion is approved by the Principle Investigator in order for a subject to be eligible for the study.
7. History of cerebrovascular accident including transient ischemic attack (TIA), pulmonary embolism or untreated deep venous thrombosis (DVT) within the past 6 months.
Note: Subjects with recent DVT who have been treated with therapeutic anti-coagulating agents for at least 6 weeks are eligible
8. Major surgery or trauma within 28 days prior to first dose of investigational product and/or presence of any non-healing wound, fracture, or ulcer (procedures such as catheter placement not considered to be major surgery).
9. Evidence of active bleeding or bleeding diathesis.
10. Known endobronchial lesions and/or lesions infiltrating major pulmonary vessels that increase the risk of pulmonary hemorrhage
11. Recent hemoptysis (** teaspoon of red blood within 8 weeks before first dose of study drug).
12. 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.
13. Unable or unwilling to discontinue use of prohibited medications in for at least 14 days or five half-lives of a drug (whichever is longer) prior to the first dose of study drug and for the duration of the study (Chapter 8.7).
14. Treatment with any of the following anti-cancer therapies:
• radiation therapy, surgery or tumor embolization within 14 days prior to the first dose of pazopanib OR
• 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
15. Administration of any non-oncologic investigational drug within 30 days or 5 half lives whichever is longer prior to receiving the first dose of study treatment
16. 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

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	17-09-2013
Enrollment:	30
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:	03-05-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	26-06-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO

Date:	16-07-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-07-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-02-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-03-2015
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	EUCTR2013-001567-24-NL
CCMO	NL44644.031.13
Other	volgt