Improving the tolerability of the oral targeted anti-cancer drug pazopanib by food intake (DIET).

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Part APrimary objective:To determine the equivalent dose of pazopanib when taken with a continental breakfast compared to 800 mg in fasted state.Secondary objective:To monitor the occurrence of adverse events of pazopanib with and without food...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON47219

Source
ToetsingOnline

Brief title
DIET

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
renal cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Apotheek
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: breakfast, pazopanib, pharmacokinetics

Outcome measures

Primary outcome

Part A

The aim of this part of the study is to determine the equivalent reduced dose of pazopanib when taken with a continental breakfast compared to the registered intake of pazopanib (e.g. 800 mg OD without food)

Part B

The aim of this part of the study is to show a decrease of the side effects, diarrhea and nausea when an pazopanib is taken with food.

Secondary outcome

Part A

To explore, quantify and describe the correlation in the occurrence of side effects when pazopanib is taken with food.

Part B

To explore, quantify and describe patients preference; pazopanib intake with or without food.

To explore the progression free survival of the total cohort of the patients and to compare this against historical data.

Study description

Background summary

Pazopanib (Votrient) is a multi targeted tyrosine kinase inhibitor of vascular endothelial growth factor receptor, (VEGFR-1, -2 en -3), platelet-derived growth factor receptor (PDGFR-* and **), and stem cell factor receptor (c-KIT). Pazopanib is registered for the treatment of patients with advanced renal cell carcinoma and patients with soft tissue sarcoma who have received prior chemotherapy. Pazopanib is administered at a fixed oral dose of 800 mg OD regardless of size, age and clinical condition. Pazopanib is absorbed from the gastrointestinal tract with an absolute oral bioavailability of ~21%.
Pazopanib is practically insoluble and highly permeable. When ingested with high fat food the pazopanib exposure (area under the concentration time curve (AUC)) is doubled. Common adverse effects are diarrhea and nausea. This might be caused by the non-absorbed proportion of pazopanib. A dose reduction when ingested with food could be a logical approach to reduce these side effects; however this is not tested in patients yet. Therefore we want to perform a bioequivalent study to investigate what dose with a continental breakfast equals the dose of 800 mg in fasted conditions (study part A). In part B of the study we want to investigate whether the intake with food reduces the frequently reported side effects.

Study objective

Part A
Primary objective:
To determine the equivalent dose of pazopanib when taken with a continental breakfast compared to 800 mg in fasted state.
Secondary objective:
To monitor the occurrence of adverse events of pazopanib with and without food according to the CTC-AE criteria v 4.03

Part B
Primary objective:
To evaluate whether a reduced pazopanib dose ingested with food can reduce the side effects diarrhea and nausea.
Secondary objective:
To evaluate the preference of the patients: intake of pazopanib with or without food.
To evaluate the progression free survival time in all patients.

Study design

Part A

Patients who use pazopanib are included.
A total of 16 - 19 patients will be included, pharmacokinetic (PK) and safety evaluation will initially be performed in three patients treated with 800 mg OD (100%) pazopanib in a fasted state for two weeks followed by two weeks of 600 mg OD (75%) pazopanib together with a standardized continental breakfast. PK assessment will be performed after 2 (800mg OD without food) and 4 weeks (600mg OD with food) of pazopanib therapy. The results of these three patients will be analysed and discussed to determine a safe and feasible dose for the next patients in the study. The dose for the next 13 * 16 patients will either be 600mg OD (75%) or 400mg OD (50%) partly based on the safety profile observed in the initial three patients, PK assessment and literature data.
After the second PK assessment all patients go back to the standard dose of 800mg OD taken without food.

Part B
Patients who use pazopanib within label are eligible for inclusion.
A total of 60 patients are included and randomized over two groups. Group 1 starts with 800 mg pazopanib in a fasted state. After one month of therapy they will switch to a reduced though equivalent dose (established in part A of the study) taken together with a continental breakfast during the next month. Group 2 starts with the reduced equivalent dose of pazopanib ingested with food and will switch after one month to 800 mg pazopanib in a fasted state. During both treatment periods diarrhea and nausea will be monitored and scored according to the CTC AEv4.03 criteria.
After each treatment period patients will be asked to complete a questionnaire regarding their pazopanib intake comfort. At the end of the study period of two months, all patients will be asked for their preference.
After the two months of observed and controlled intake of pazopanib patients will continue pazopanib therapy at the standard dose taken in fasted state until they do no longer have clinical benefit from the therapy.

Study burden and risks

In general the risk for participation in this study is regarded low. If no bio* equivalent exposure is reached when ingested with food, patients get a sub-optimal treatment for only two weeks The risk of suboptimal dosing is minimized by the run in of three patients at 600 mg OD with food. Heath et al showed that pazopanib ingestion with food increases bioavailability with 200%. The continental breakfast in this study contains half the amount of fat compared to the FDA meals Heath et al used (4). Therefore, we will start to test a dose reduction of 25 % instead of 50% in a small number of three patients to prevent under dosing. After a short period of two weeks, PK assessments will be preformed to monitor the potential risk of under or over dosing. . However if this occurs this is for only a short period of time in part A (2 weeks). This short period of potential suboptimal dosing will not affect the treatment outcome .

Benefits for patient participating in part A will be regarded low.
Participants in part B will probably experience less side effects and the intake of pazopanib will be more easily incorporated in their normal life style.

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.
2) * 18 year old men and women who use pazopanib
3) Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.

Exclusion criteria

1) Clinically significant gastrointestinal abnormalities that may affect absorption of investigational product including,
2) 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.
3) Unable or unwilling to discontinue use of prohibited medications
4) Concurrent use of other substances known or likely to interfere with the pharmacokinetics of pazopanib.

Study design

Design

Study type:	Observational invasive
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-06-2014
Enrollment:	79
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	12-12-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-03-2014
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-07-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-09-2018
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2013-004108-20-NL
CCMO	NL46463.091.13

Study results

Date completed:	09-08-2018
Actual enrolment:	97