A single arm Pharmacokinetic/Pharmacodynamic Study of Sunitinib and Pazopanib in Patients with Metastasized Renal Cell Carcinoma

Published: 02-07-2014
Last updated: 20-04-2024

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Observational non invasive

Summary

ID

NL-OMON40825

Source
ToetsingOnline

Brief title
EuroTARGET substudy/(EuT-PK/PD)

Condition

- Renal disorders (excl nephropathies)

Synonym
advanced kidney cancer + metastatic renal cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: European Commission under the Seventh Framework Programme (FP7)

Intervention

Keyword: pazopanib, pharmacodynamics, pharmacokinetics, sunitinib

Outcome measures

Primary outcome

For development of the pharmacokinetic/pharmacodynamic model, for every patient a maximu of 12 blood samples will be taken within the time frame of this study and within 3 cycles of sunitinib treatment or within 18 weeks of pazopanib treatment. These blood samples will be used to determine the blood plasma levels for sunitinib, the active metabolite of sunitinib (SU12662), pazopanib and VEGFR2 and VEGFR3. Further, there will be blood pressure measurements at regular intervals. Demographic and patient specific data will be completed in electronical Case Report Forms (CRFs) as a part of the total EuroTARGET project. After completion of the PK/PD model de blood samples will be used to extract DNA and to determine patient specific genotypes. These genotypes will be used as covariates in the PK/PD model.

Secondary outcome

N/A

Study description

Background summary

Kidney cancer is one of the most common cancer types in Europe with 88,400 new cases and 39 400 deaths in 2008. Nearly 90% of those cases are renal cell carcinomas. While mortality constantly decreases concerning better diagnosis and treatment, the prognosis with diagnosed renal cell carcinoma is still poor. A therapy of renal cell carcinoma with established anticancer agents is not successful as the pathology of this kind of cancer cells includes a high expression of P-glycoprotein conferring a multi drug resistance. Before the introduction of antiangiogenic treatment the only available systemic therapy for metastasized renal cell carcinoma (mRCC) patients was a cytokine-therapy with high dose interleukin-2 or interferon-alpha treatment in combination with surgical ablation of metastases, if possible. With the understanding of the basic mechanism of RCC genesis, a big step ahead was made on the way to targeted therapy. Tumours need an autonomous blood supply to continue growing. Therefore, they release several growth factors to stimulate the genesis of new blood vessels.
The genes involved in these processes vary between different histological types of RCC. Most common is the so called clear cell carcinoma which accounts for 75% of all RCC. Here, the cause of the increased angiogenesis is the inactivation of the von Hippel-Lindau gene which causes an accumulation of hypoxia-inducible factor (HIF) and leads to an over expression of angiogenic factors such as vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). These proteins bind to receptors on the surface of endothelial cells where they stimulate angiogenesis. This led to the development of drugs which specifically target the process of angiogenesis.
In 2005 the first antiangiogenic agent was introduced onto the market, bevacizumab (Avastin®), a monoclonal anti body against VEGF. The combination of interferon-alpha and bevacizumab showed a significant improvement in terms of progression-free survival (PFS) over the previously used mono therapy with interferon only. Since the introduction of the multiple-tyrosine-kinase inhibitors sunitinib (Sutent®) and sorafenib (Nexavar®) in 2006 a potent oral antiangiogenic therapy of mRCC is available. The decision which antiangiogenic agent is chosen depends on the Motzer-criteria to predict survival of patients with advanced RCC. While sunitinib is indicated as first-line therapy for low or medium-risk mRCC patients, sorafenib is only second line for patients who already received a cytokine-treatment.

Sunitinib
Sunitinib is an inhibitor of several receptor-tyrosine kinases which are associated with angiogenesis and the growth of metastases. Sunitinib inhibits platelet-derived growth factor (PDGF) receptor α and β, vascular endothelial growth factor (VEGF) receptor 1-3, the KIT (stem cell factor)-receptor, Fms-like tyrosine kinase 3 (FLT) receptor, the colony stimulating factor 1 (CSF 1) receptor as well as the *rearranged during transfection* (RET) receptor.
Sunitinib is primarily metabolized by Cytochrome P450 A4 which leads to the active metabolite N-desethyl-sunitinib (SU12662). The metabolite shows similar pharmacodynamic and pharmacokinetic effects and is responsible for 23 to 27 % of total drug exposure. The volume of distribution is about 2230 L, the

elimination half-life approximately 40 to 60 h and 80 to 110 h for the active metabolite.

Pazopanib
Pazopanib is an oral multi-tyrosine kinase inhibitor which targets VEGF receptor -1, -2 and- 3, PDGFR-alfa and -beta as well as *stem cell factor* -receptor (c-KIT). Pazopanib is primarily metabolized by CYP3A4 and partly by CYP1A2 and CYP2C8. There are four metabolites which only contribute for 6% of the overall exposure. In-vivo binding to human plasma proteins is higher than 99% which results in a large volume of distribution. Excretion is primarily via feces with renal elimination accounting for only < 4%. The elimination half-life is about 30.9 h.

Study objective

The primary goal of this research is to develop a pharmacokinetic/pharmacodynamic (PK/PD) model for sunitinib and pazopanib in patients with metastatic renal cell carcinoma, so that the possible use of biomarkers can be tested as predictors for the treatment outcome for individual patients. These biomarkers could be: blood pressure, sVEGFR2 and sVEGFFR3. Furthermore, there will be investigations on the extent to which patient specific data, so called covariates, such as age, weight, disease status, several genotypes, organ function or compliance could influence pharmacokinetic and pharmacodynamic parameters and thereby the result of therapy outcome.

Study design

Single-arm, phase IV study in patients with metastatic renal cell carcinoma and a planned first-line treatment with either sunitinib (Sutent®) or pazopanib (Votrient®). This research is performed as a substudy of EuroTARGET as a non-interventional EuroTARGET study.

Study burden and risks

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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

- female or male patients of 18 years of age or older
- diagnosed with metastatic renal cell carcinoma and not yet having received treatment for their disease in the metastatic setting
- first-line treatment with either sunitinib or pazopanib

Exclusion criteria

- unable to read or understand the patient information and informed consent form
- existing contraindication for sunitinib or pazopanib

Study design

Design

Study phase:	4
Study type:	Observational non invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-07-2014
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO

Date:	02-07-2014
Application type:	First submission
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	EUCTR2012-001415-23-NL
CCMO	NL48521.058.14