An intervention study of the effects of probenecid on the pharmacokinetics and pharmacodynamics of sorafenib (PROSORA-study)

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To demonstrate the bioequivalence of sorafenib with probenecid relative to sorafenib without probenecid based on the AUC in patients with unresectable hepatocellular cancer, advanced clear-cell renal cell carcinoma, locally recurrent or metastatic,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatobiliary neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46801

Source
ToetsingOnline

Brief title
PROSORA-study

Condition

- Hepatobiliary neoplasms malignant and unspecified

Synonym
differentiated thyroid carcinoma, Hepatocellular carcinoma, metastatic renal cell carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

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

Intervention

Keyword: HFSR, pharmacokinetics, Probenecid, Sorafenib

Outcome measures

Primary outcome

To demonstrate the bioequivalence of sorafenib with probenecid relative to sorafenib without probenecid based on the AUC in patients with unresectable hepatocellular cancer, advanced clear-cell renal cell carcinoma, locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment.

Secondary outcome

1. Other pharmacokinetic outcomes (i.e. clearance, maximum concentration (Cmax), Maximum steady-state concentration (Cmaxss), Minimal concentration (Cmin), steady-state volume of distribution (Vss) and half-life (t*)).

2. To evaluate the incidence and severity of side-effects of treatment with sorafenib in absence and presence of probenecid (in particular HFSR) .

3. To evaluate the intracellular concentration of sorafenib in skin in patients treated with sorafenib in absence and presence of probenecid.

4. to determine the influence of HFSR on quality of life

Study description

Background summary

In oncology, the last two decades have seen a transition from the use of traditional cytotoxic chemotherapy to the emergence of a new paradigm in

rational drug design coupled with an uprising in the development of targeted agents, including the kinase inhibitors. However, while kinase inhibitors possibly offer a number of important theoretical advantages over conventional cytotoxic chemotherapy, they are still afflicted by some of the same problems, including an extensive interindividual pharmacokinetic variability, the existence of a rather narrow therapeutic window, and the occurrence of multiple, debilitating adverse events.

Cutaneous adverse effects are among the most frequently observed toxicities with many kinase inhibitors, and their intensity can significantly affect both quality of life and health care economics. A particularly painful complication seen most frequently during the early weeks of use with multikinase inhibitors (MKIs), such as sorafenib, sunitinib, and pazopanib, is called hand-foot skin reaction (HFSR), in which hyperkeratotic plaques develop predominantly over sites of pressure or friction. These plaques may have significant inflammation and xerotic hyperkeratosis, often in a bilateral symmetric distribution, causing pain and debilitation that interfere with activities of daily living. Sequential biopsy specimens have revealed progressive accumulation of hyperkeratosis with focal parakeratosis. The clinical incidence of HFSR varies among MKIs with a particularly high incidence being observed with sorafenib and does not appear to be related to increased excretion of MKIs through sweat.

Sorafenib is an orally administered MKI with activity against VEGFR-2, VEGFR-3, Flt-3, RAF-1 and c-KIT. Phase III clinical trials demonstrated the efficacy of sorafenib in advanced hepatocellular carcinoma, advanced renal cell carcinoma as well as iodine-refractory advanced thyroid cancer. After oral administration sorafenib undergoes CYP3A4 mediated oxidation into its active metabolite (pyridine-N-oxide) and UGT1A9-mediated glucuronidation into sorafenib glucoronide. Sorafenib is eliminated for 77% via the feces of which 51% as unchanged drugs. Excretion of glucuronidated metabolites in urine accounts for 19% of the total elimination.

The pathogenesis of MKI-induced HFSR remains currently unknown, and the only demonstrably effective treatment options involve dose reduction or discontinuation of therapy, which have negative effects on disease management.(7, 8) Furthermore, sorafenib can extensively accumulate into human epidermal keratinocytes mediated by the organic anion transporter SLC22A20 (OAT6). In vivo research in mice demonstrated that this effect can be reversed by cotreatment with the OAT6 inhibitor probenecid.
Probenecid is a uricosuric agent indicated for the maintenance treatment of hyperuricemia associated with gout and gouty arthritis. Sometimes it is used as an adjuvant for therapy with certain antibiotics as penicillin, ampicillin or methicillin, because it elevates and prolongs their plasma levels. Probenecid is usually well tolerated in a dose of 500 mg two times daily and is normally

taken for (many) months. Probenecid also acts as a pan-UGT inhibitor by inhibiting multiple UDP-glucuronosyltransferase enzymes (UGT1A1, 1A6, 1A7, 1A9, 1A10, 2B7) and therefore potentially could influence sorafenib pharmacokinetics. The extent of this effect is not yet determined in clinical studies.

In this study we therefore want to study the safety and pharmacokinetics (PK) of sorafenib when concomitantly used with probenecid by human objects. If no PK interactions are observed, this pharmacotherapeutic intervention may provide a potential treatment strategy for sorafenib-induced HFSR. As a secondary endpoint we therefore want to look at the incidence of all-grade HFSR and intracellular concentration of sorafenib in skin.

Study objective

To demonstrate the bioequivalence of sorafenib with probenecid relative to sorafenib without probenecid based on the AUC in patients with unresectable hepatocellular cancer, advanced clear-cell renal cell carcinoma, locally recurrent or metastatic, progressive, differentiated thyroid carcinoma refractory to radioactive iodine treatment.

Secondary outcomes are:
1. Other pharmacokinetic outcomes (i.e. clearance, maximum concentration (Cmax), Maximum steady-state concentration (Cmaxss), Minimal concentration (Cmin), steady-state volume of distribution (Vss) and half-life (t*)).
2. To evaluate the incidence and severity of side-effects of treatment with sorafenib in absence and presence of probenecid (in particular HFSR) .
3. To evaluate the intracellular concentration of sorafenib in skin in patients treated with sorafenib in absence and presence of probenecid.
4. To determine the influence of HFSR on quality of life.

Study design

This is a non-randomized, single-center, prospective pharmacokinetic interventional drug-drug interaction cohort study in patients taking probenecid and sorafenib to evaluate the pharmacokinetics (PK) and safety of sorafenib concomitantly used with probenecid in patients with histologically or cytologically confirmed diagnosis of metastatic renal cell carcinoma, hepatocellular carcinoma or differentiated thyroid carcinoma. This study will be performed at the Erasmus MC Cancer Institute in Rotterdam, The Netherlands. It is anticipated that
sorafenib treatment must have been initiated at least 7 days prior to start of the study, but no longer than 14 days. to ensure steady-state concentration of sorafenib during the study period. It is anticipated that the study will be completed within 12-18 months after approval of the ethical board

Patients will be admitted to the hospital for pharmacokinetic (PK) blood sampling at Day 1. During this admission blood samples are drawn up to 12 hours after start of sorafenib administration and a single biopsy of the skin will be performed. 12 hours after start of sorafenib PK sampling patients will start with oral administration of probenecid. Patients will be re-admitted to the hospital for a second PK sampling at Day 15. If patients have given consent for an additional skin biopsy an extra biopsy of the skin of the hand or an active HFSR lesion will be performed for pathologic grading.

Intervention

Probenecid concomitant with sorafenib during 2 consecutive weeks

Study burden and risks

Patients will be admitted to the hospital for 12 hours on two different PK days, during which 9 pharmacokinetic blood withdrawals and one biopsy will be performed. Patients do not benefit individually from this study. Risks to be expected are *normal* side effects of sorafenib and probenecid for which patients will be carefully observed .

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. Age * 18 years
2. Histological or cytological confirmed diagnosis of mRCC, HCC or differentiated thyroid carcinoma
3. Start of sorafenib therapy, at least 7 days but nog longer than 14 days prior to start of the study NB. Patients are allowed to have had previous sorafenib therapy or have started with sorafenib.
4. WHO Performance Status * 2 (appendix D)
5. Able and willing to sign the Informed Consent Form prior to screening evaluations
6. Adequate organ function as defined by
a. Adequate liver function before start of sorafenib (to be determined by the oncologist)
b. Serum creatinin * 1.5 x ULN
7. Adequate baseline patient characteristics (complete blood count, and serum biochemistry which involves sodium, potassium, creatinin, calculation of creatinin clearance (MDRD), amylase, lipase, calcium, phosphate, AST, ALT, gamma glutamyltranspeptidase (*-GT), lactate dehydrogenase (LDH), ALP, total bilirubin, albumin).

Exclusion criteria

1. Use of drugs which may show an increased systemic exposure when taken concomitantly with probenecid. (see appendix C)
2. Patients with known blood dyscrasias, uric acid kidney stones or until an acute gouty attack has subsided.
3. Use of (over the counter) medication or (herbal) supplements which can interact with either sorafenib or probenecid, e.g. by induction or inhibition of CYP3A4, UGT1A9 (see appendix B and C)
4. Unable or unwilling to abstain from grapefruit, grapefruit juice, herbal dietary supplements, and herbal tea during the study
5. Previous use of probenecid during the last 2 weeks prior to sorafenib treatment
6. Contraindications for use of probenecid such as acute gouty attack or porphyria.
7. Unwilling to undergo a skin biopsy
8. Body mass index (BMI) beneath 8.5 or above 35

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-02-2018
Enrollment:	16
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Nexavar
Generic name:	Sorafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Probenecide
Generic name:	Probenecide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-08-2017
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2017-002470-40-NL
CCMO	NL62522.078.17