Onderzoek naar het effect van OATP1B blokkade op de stofwisseling van sorafenib (Nexavar®) bij volwassen patiënten met kanker.

Gepubliceerd: 08-08-2013 Laatst bijgewerkt: 18-08-2022

Recent pre-clinical experiments demonstrated that sorafenib in Oatp1b2(-/-) mice had 8-fold increased sorafenib-glucuronide blood concentrations.OATP1B1 and 1B3 are highly expressed in the human liver and facilitate the hepatocellular uptake of...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON23851

Bron
NTR

Verkorte titel
SORA-RIFA

Aandoening

Solid tumors treated with sorafenib (Nexavar®) mono therapy.

Ondersteuning

Primaire sponsor: Erasmus Medical Center; Department of Medical Oncology
Overige ondersteuning: Erasmus Medical Center; Department of Medical Oncology

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To determine the influence of OATP1B inhibition, through rifampicin exposure, on the metabolism and plasma pharmacokinetics of sorafenib and its metabolites.

Toelichting onderzoek

Achtergrond van het onderzoek

Rationale: Sorafenib is a multi-targeted tyrosine kinase inhibitor, which has been approved for irresectable hepatocellular carcinoma (HCC) and advanced renal cell carcinoma (RCC). It is known that sorafenib is predominantly metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and UDP-glucuronosyltransferase 1A9 (UGT1A9). In pre-clinical research mice with mutated organic anion transporting polypeptides (OATP) 1B2 prove to have an eight-fold increase of sorafenib plasma concentrations. Therefore this study aims to observe the effect of these transporters on sorafenib metabolism by inhibiting it with rifampicin and by analyzing germline pharmacogenetics of the OATP genes.

Objective: Primary objective is to determine the influence of OATP1B inhibition, through rifampicin exposure, on the metabolism and plasma pharmacokinetics of sorafenib and its metabolites.

Secondary objectives are to compare the incidence and severity of side effects of treatment with sorafenib in the absence and presence of rifampicin (interim-analysis after 4 patients), to study the influence of genetic polymorphisms in OATP1B involved in the metabolism of sorafenib, according to protocol METC 02.1002, and to assess the degree of CYP3A induction after administration of rifampicin for two days by measuring midazolam clearance.
Study design: This is a single- center, randomized cross- over pharmacokinetic study.

Study population: Patients will be recruited from a population of cancer patients with solid tumors treated with sorafenib.
Intervention: Patients that are regularly treated with sorafenib for at least 14 days will be admitted to the hospital for pharmacokinetic blood sampling on day 2 and day 11. Patients will receive rifampicin 600 mg orally prior to the pharmacokinetic blood sampling on days 1 and 2 in arm A and on days 10 and 11 in arm B, in order to assess the influence of OATP1B blockage on sorafenib pharmacokinetics. Furthermore, patients will be challenged with a midazolam test (2,5 mg intravenously) during each hospital admission in order to assess the degree of CYP3A induction due to rifampicin.
Main study parameters/endpoints: As primary endpoint, pharmacokinetics of sorafenib with and without preceding OATP1B inhibition by rifampicin will be compared. Secondary endpoints include the analysis of side effects after rifampicin administration and the influence of germline genetic polymorphisms in OATP1B on sorafenib pharmacokinetics. Finally, CYP3A

induction due to rifampicin will be assessed by observing the clearance of midazolam. Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Patients on regular treatment with sorafenib will be admitted to the hospital on two different days, during which pharmacokinetic blood withdrawals and a midazolam clearance test (MCT) will be performed. In advance of one of the hospital admissions (depending on randomization), patients are challenged with rifampicin 600 mg on two consecutive days. Patients do not benefit individually from this study. Major risks to be expected are side effects of one of the investigational medicinal products, for which patients will be carefully observed.

Doel van het onderzoek

Recent pre-clinical experiments demonstrated that sorafenib in Oatp1b2(-/-) mice had 8-fold increased sorafenib-glucuronide blood concentrations.OATP1B1 and 1B3 are highly expressed in the human liver and facilitate the hepatocellular uptake of several substrates before metabolism and efflux from the liver. Because sorafenib is subject to an enterohepatic recirculation, OATP1B deficiency in human possibly results in altered sorafenib (parent drug) concentrations. If rifampicin is used as OATP inhibitor, and not as CYP3A4 inducer, sorafenib concentrations may increase indirectly. This study should help to provide further insights into the variability in antitumor activity and side effects in sorafenib-treated patients.

Onderzoeksopzet

Within 2 weeks patients will be admitted twice for pharmacokinetic sampling

Onderzoeksproduct en/of interventie

1. Administration of rifampicin and midazolam.

2. Bloodwithdrawal for pharmacokinetics of sorafenib and midazolam.

Contactpersonen

Publiek

Erasmus MC Rotterdam – Daniel den Hoed Cancer Center
Department of Medical Oncology
 Room G4-80
Ron H.J. Mathijssen
Groene Hilledijk 301
Rotterdam 3075 EA
The Netherlands
+31 (0)10 7041338, buzzer 229

Wetenschappelijk

Erasmus MC Rotterdam – Daniel den Hoed Cancer Center
Department of Medical Oncology
 Room G4-80
Ron H.J. Mathijssen
Groene Hilledijk 301
Rotterdam 3075 EA
The Netherlands
+31 (0)10 7041338, buzzer 229

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

• Age ≥18 years;

• Histological/ cytological confirmed diagnosis of cancer treated with sorafenib monotherapy

• Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 to 1. (see appendix A);

• A stable dose of sorafenib for at least 2 weeks (to guarantee steady-state);

• Adequate hematological functions, absolute neutrophil count (ANC)> 1.0 x 109/L, platelet count ≥ 100 × 109/L);

• Adequate renal and hepatic functions defined as serum creatinin <1.25 x ULN; total bilirubin <1.25 x ULN; asparate aminotransferase (AST) and alanine aminotransferase (AST) ≤ 5 x ULN;
• PTT ≤ 1.5×ULN and INR < 1.5;

• Signed informed consent and amenable to compliance with protocol schedules and testing;

• For patients with reproductive potential a reliable method of contraception (excluding oral contraceptive) must be used.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

A potential subject who meets any of the following criteria will be excluded from participation in this study:

• Pregnant or child nursing patients;

• Serious illness or medical unstable condition requiring treatment, symptomatic CNS-metastases or history of psychiatric disorder that would prohibit the understanding and giving of informed consent;

• Major surgery within 2 weeks prior to start of the protocol;

• Radiotherapy within the last 2 weeks before start of this study;

• Patients who had a liver transplantation prior to sorafenib treatment;

• Patients who receive therapeutic anticoagulation therapy. Low dose, non- therapeutic anticoagulation (e.g., low dose warfarin) for catheter prophylaxis only will be permitted;

• Patients who receive anti-retroviral therapy for Human Immunodeficiency Virus (HIV). Prophylactic antiviral therapy to prevent Hepatitis B virus (HBV) reactivation or cytokine therapy (e.g. interferon) for Hepatitis C virus infection is allowed;

• Use of CYP3A4 inhibiting or inducing medication;

• Concurrent medication or supplements which can interact with sorafenib.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Cross-over
Toewijzing:	Gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	12-08-2013
Aantal proefpersonen:	9
Type:	Werkelijke startdatum

Ethische beoordeling

Positief advies

Datum:	08-08-2013
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3945
NTR-old	NTR4110
Ander register	MEC ErasmusMC : MEC 2013-194
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten
N/A