CYP3A4*22 genotype-guided dosing of TKIs in cancer patients: a new way of personalized therapy

Gepubliceerd: 11-02-2019 Laatst bijgewerkt: 18-08-2022

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

Samenvatting

ID

NL-OMON25948

Bron
Nationaal Trial Register

Verkorte titel
STAR22

Aandoening

Cancer, neoplasm

Ondersteuning

Primaire sponsor: Erasmus MC
Overige ondersteuning: De Merel stichting

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

To demonstrate that a dose reduction of 20-33% of CYP3A4 metabolized tyrosine kinase inhibitors in patients expressing the CYP3A4*22 gene (rs35599367 C>T in intron 6) does not result in a lower exposure (Ctrough) than the wildtype group with the usual dose.

Toelichting onderzoek

Achtergrond van het onderzoek

Since a few decades, tyrosine kinase inhibitors (TKI) are widely used for the treatment of cancer. These type of drugs are predominantly metabolized by CYP3A4. CYP3A4 activity is highly variable among patients since it could vary 10-100 times between individuals. Since the expression of CYP3A4 mRNA is significantly correlated with the protein expression of CYP3A4, CYP3A4*22 will also lead to a lower level of CYP3A4 protein.
For this reason CYP3A4*22 variant carriers have less functional CYP3A4 enzyme which results in higher systemic exposure and less clearance of drugs. Recent publications demonstrated that the clearance of pazopanib and sunitinib is lowered because of the CYP3A4*22 variant. Therefore our hypothesis is that the exposure of CYP3A4*22 carriers is not lowered when patients are dosed with 66%-80% of the registered dose compared to the control group.

In short, in previous studies is proven that CYP3A4*22 results in a lower clearance of TKIs metabolised by CYP3A4*22 and even can result in a higher exposure when a drug is metabolised bij CYP3A4. A higher exposure can lead to a higher incidence of toxicities caused by the drug. Due to this quality of life could be lowered for a patient. Moreover, there is a chance that the treatment for this patient has to be stopped because of the toxicity experienced by the patient. If there is evidence that CYP3A4*22 carriers have at least the same exposure when they are treated with a dosereduction of 25-33%, a relative simple intervention could realize
a effective treatment with a lower chance of adverse events and toxicity.

Doel van het onderzoek

The aim of the study is to show that patients with the *22-variant can be safely given a lower dose of medication (i.e. ~75%) without a decrease in exposure compared to patients without the *22-variant who receive the standard dose of medication (i.e. 100%).

Onderzoeksopzet

Steady-state

Contactpersonen

Publiek

Erasmus MC
Ruben van Eerden

0107039640

Wetenschappelijk

Erasmus MC
Ruben van Eerden

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

1. Indication to start treatment with TKI which is mainly metabolised by CYP3A4;
2. Proven malignancy;
3. Age > 18 years;
4. Able and willing to give written informed consent;
5. WHO performance status of 0, 1 or 2;
6. Able and willing to undergo blood sampling for PK and genetic analysis;

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. Pregnant or lactating women;
2. Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair treatment compliance;
3. Serious illness or medical unstable condition prohibiting adequate treatment and follow-up.
4. Unable or unwilling to stop the use of (over the counter) medication or (herbal) supplements which are known or suspected to strongly inhibit or induct the CYP3A4 enzymes;

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Niet-gerandomiseerd
Blindering:	Open / niet geblindeerd
Controle:	Actieve controle groep

Deelname

Nederland

Status:	Werving gestart
(Verwachte) startdatum:	11-02-2019
Aantal proefpersonen:	198
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	11-02-2019
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	NL7514
Ander register	METC Erasmus MC : METC2018-1538 or NL67818.078.18

Resultaten