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

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON25948

Source
Nationaal Trial Register

Brief title
STAR22

Health condition

Cancer, neoplasm

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: De Merel stichting

Intervention

Outcome measures

Primary outcome

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.

Secondary outcome

- To compare toxicity grades (based on CTCAE) between carriers and non-carriers
- After pharmacokinetic assessment the dose may be adjusted based on clinical presentation and opinion of the treating clinician; incidence of dose modifications after four weeks will be compared using descriptive statistics between carriers and non-carriers.

Study description

Background summary

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.

Study objective

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%).

Study design

Steady-state

Contacts

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Eligibility criteria

Inclusion criteria

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;

Exclusion criteria

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;

Study design

Design

Study type: Interventional

Intervention model:	Parallel
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-02-2019
Enrollment:	198
Type:	Anticipated

IPD sharing statement

Plan to share IPD: No

Ethics review

Positive opinion

Date:	11-02-2019
Application type:	First submission

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
NTR-new	NL7514

Register	ID
Other	METC Erasmus MC : METC2018-1538 or NL67818.078.18

Study results