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

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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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON45864

Source
ToetsingOnline

Brief title
STAR22 study

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
cancer, Neoplasm

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: De Merel stichting

Intervention

Keyword: Cytochrome P-450 CYP3A, Neoplasm, Pharmacokinetics, Tyrosine kinase inhibitor

Outcome measures

Primary outcome

To compare the Ctrough after 3-4 weeks (depending on drug) of treatment (or the latest moment possible in case of toxicity or treatment discontinuation) between the CYP3A4*22 carrier group and wild type patients.

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 toxicity; incidence of dose modifications after four weeks will be compared using descriptive statistics between carriers and non-carriers.

Study description

Background summary

CYP3A4 is part of the CYP enzyme family which is responsible for the metabolism of 45-60% of the prescribed drugs. CYP3A4 forms the major part of the cytochrome P450 enzyme family.

Wang et al. first described a new polymorphism in the CYP3A4 gene, rs35599367 or CYP3A4*22. CYP3A4*22 is caused by a transition from a cytosine into a thymine in intron 6 which is located 192 bp upstream of exon 7 of the CYP3A4 gene (position 15389 in intron 6 of CYP3A4) which results in less activity of CYP3A4 in the liver. Due to this transition the formation of a non-functional splice variant (aSV) of CYP3A4 is increased. The partial retention of intron 6 result in the production of truncated CYP3A4 mRNA and therefore also less production of full-length and functional CYP3A4 mRNA. The allelic frequency for this SNP is 5,0% in Europeans, 2.6% in the admixed American population, 0,6% in the South Asian population, 0% in East Asians and <0,1% in Africans.

In the preceding years several studies has been performed investigating the effect of CYP3A4*22 on the pharmacokinetics of drugs metabolised by CYP3A4 in patients diagnosed with cancer. A retrospective analysis in patients treated with the TKI sunitinib showed a 22.5% decrease in the clearance of sunitinib in CYP3A4*22 carriers versus non-carriers. Another study concluded that CYP3A4*22 carriers treated with the TKi pazopanib have a significant and clinical relevant lower clearance and therefore higher exposure. Moreover, the performed simulations showed that trough concentrations at steady state were 50% higher in CYP3A4*22 carriers.

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

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. If our hypothesis has been confirmed, in the future CYP3A4*22 carriers could safely be treated with a lower dose without losing exposure compared to non-carriers and most importantly, severe toxicity may be prevented in CYP3A4*22 carriers.

Study design

Prospective multi-centre non-randomized non-inferiority intervention study

Intervention

Patients intended to be treated with one of the participating drugs will be prospectively genotyped for CYP3A4*22. Patients that prove to be wildtype will be treated with the standard-dose treatment. In patients homozygous or heterozygous polymorphic for CYP3A4*22 a 20-33% dose reduction during 3-4 weeks (depending on drug) will be applied. Based on clinical tolerability and opinion of the clinician the dose may be adjusted after the end of study.

Study burden and risks

In order to determine the CYP3A4*22 genotype prior to the start of therapy, blood will be drawn from the patients which are intended to be treated with one of the participating drugs and have signed the informed consent. This will not require an extra venepuncture, as it is combined with other standard laboratory pre-treatment tests. Therefore, the risk and burden associated with genotyping is minimized.

The pharmacogenetic analysis may cause a small delay in the start of treatment. However this analysis will be performed every week so this will be for a very short period which is unlikely to be clinical relevant. Moreover between the first visit and start of treatment patients are discussed in a multidisciplinary board. In this period the logistics of the study could already begin and the delay will be further reduced.

Since a dose reduction is performed there is a small risk patients are underdosed. However, recent studies conclude that the exposure in CYP3A4*22 carriers is higher compared to wild type patients and therefore the risk that patients are under dosed is limited. Moreover, the time of the dose reduction is short (maximum of 4 weeks), dose reductions are often performed in clinical practice in case of toxicity, we expect the same increase of drug exposure from CYP3A4*22 carriers as from CYP3A4 inhibitors, which is from all the participating drugs higher than a 25% increase and it is hypothesized that genotype-guided dosing improves patient safety of treatment by reducing the risk of severe toxicity and toxicity-associated hospitalization. Based on clinical tolerability and opinion of the clinician the dose may be adjusted after the end of study.

After steady state, a blood sample will be drawn for pharmacokinetic analysis. There is no significant risk associated with this venepuncture, besides a small risk of pain, bruises or thrombophlebitis, which is similar to the risk of other venepunctures performed during routine treatment of the patient. If possible, this venepuncture will be combined with a venepuncture for routine care.

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. Indication to start treatment with TKI which is preliminary 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 phase:	4
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-03-2019
Enrollment:	198
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Cabometyx
Generic name:	Cabozantinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cotellic
Generic name:	Cobimetinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sprycel
Generic name:	Dasatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tafinlar
Generic name:	Dabrafenib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tarceva

Generic name:	Erlotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-11-2018
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-08-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-12-2020
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	EUCTR2018-003954-26-NL
CCMO	NL67818.078.18