A Prospective, multicenter, observational study to identify deleterious novel variants of the DPYD gene in patients of non-Western descent: The DPYD-NOW study

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Primary objective:To identify novel variants in the DPYD gene in non-Western patients that are related to the occurrence of severe (grade *3) toxicity upon treatment with fluoropyrimidines.Secondary objective:* To determine the influence of novel...

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

Summary

ID

NL-OMON49023

Source
ToetsingOnline

Brief title
Indentifying variants of DPYD in patients of non-Western descent

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer (breastcancer, colorectal cancer, gastric cancer)

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Stichting Fonds Oncologie Holland (SFOH)

Intervention

Keyword: DPYD, Ethnicity, Fluoropyrimdines, Genotyping

Outcome measures

Primary outcome

The primary endpoint in this study is the identification of novel variants in the DPYD gene in patients of non-Western descent that are associated with the development of severe (grade * 3) fluoropyrimidine-related toxicity and a reduced DPD enzyme activity measured in PBMCs.

Secondary outcome

* The influence of novel DPYD variants on the variation in DPD enzyme activity measured in PBMCs.

* The ability of the DPYD-varifier to predict if novel variants are deleterious

* The frequencies of DPYD variants per ethnic origin

* Exploration of additional genes related to severe fluoropyrimidine-related toxicity

Study description

Background summary

The fluoropyrimidine anticancer drugs 5-fluorouracil (5-FU) and capecitabine are standard of care in the treatment of early and advanced breast, colorectal and gastric cancer. There is ample evidence demonstrating that variation in activity of the fluoropyrimidine-metabolizing enzyme dihydropyrimidine dehydrogenase (DPD), encoded by the gene DPYD, causes clinically significant

differences in sensitivity to the toxic effects of 5-FU and capecitabine. DPD deficiency, occurring in up to 5% of the population, is associated with the risk of severe, potentially lethal, toxicity. It was shown by our group that the risk of severe fluoropyrimidine related toxicity in patients with a deleterious Single Nucleotide Polymorphism (SNP) in DPYD (i.e. a SNP that reduces enzyme activity), (DPYD*2A, c.2846A>T, c.1236G>A and 1679T>G) was significantly reduced when upfront screening of the DPYD gene and DPYD-guided dose individualization was applied. Recently, it was shown that these 4 DPYD variants are not predictive for toxicity in patients of African descent. Twelve novel non-synonymous variants were identified, seven of which significantly decreased DPD activity in vitro, in 588 patients of either Somalian or Kenyan descent. The commonly reported toxicity-associated variants DPYD*2A, c.2846A>T and c.1679T>G were not detected in any of the Somalian or Kenyan individuals. A large portion of the population (> 1.5 million) in the Netherlands is of non-western descent. The five largest groups of non-western descent in the Netherlands are of Turkish (397,000), Moroccan (386,000), Indonesian (366,800), Surinamese (349,000) and Antillean (151,000) descent. These groups will most likely carry different and possibly clinically relevant variants in the DPYD gene than the four variants (DPYD*2A, c.2846A>T, c.1236G>A and 1679T>G) that currently routinely screened for in clinical practice. This can result in unidentified DPD-deficient patients being treated with a full dose of capecitabine or 5-FU, which can lead to severe toxicity, caused by the lack of adaptive dosing guided by these variants of DPYD in the non-Western population. In this study we plan to investigate which variants in the DPYD gene are of relevance for the population of non-Western descent living in the Netherlands. We expect to find that approximately 5-8% of this population of patients will have a partial DPD deficiency, significantly affecting fluoropyrimidine clearance. Furthermore, we expect to find 5-10 new variants in the DPYD gene, of which some variants are associated to the development of severe fluoropyrimidine-related toxicity. Novel deleterious variants in DPYD could be added to the current routinely used DPYD screening panel. We expect that an extended screening panel will lead to less severe toxicity, hospital admissions and reduced risk of death, a better quality of life during and after fluoropyrimidine treatment and will be cost saving.

Study objective

Primary objective:
To identify novel variants in the DPYD gene in non-Western patients that are related to the occurrence of severe (grade *3) toxicity upon treatment with fluoropyrimidines.
Secondary objective:
* To determine the influence of novel DPYD variants on the variation in DPD enzyme activity measured in peripheral blood mononuclear cells (PBMCs);
* To determine the ability of the DPYD-varifier to predict if novel variants are deleterious;
* To determine the frequencies of DPYD variants per ethnic origin;

* To explore the relationship between genetic variants in additional genes other than DPYD and fluoropyrimidine-related toxicity

Study design

The study will last for about 24 months. Approximately 600 patients will be included. An overview of the study design can be seen in Figure 1. This is a prospective, multicenter observational study, that will be performed in multiple centers in the Netherlands. The DPYD gene of patients of non-Western descent eligible for treatment with capecitabine or 5-FU in the participating centers will be sequenced. Afterwards, the sequencing data will be compared to the data of Western patients with sequencing data from the KWF/Alpe study (n=1103) (NCT02324452). Furthermore, the DPD enzyme activity in PBMCs of all patients will be determined. Novel DPYD variants that are associated with low DPD enzyme activity in PBMCs and the development of CTCAE (version 5.0) grade * 3 toxicity will be classified as deleterious. For DPYD variants found to be associated with low DPD enzyme activity but without leading to severe toxicity, additional testing will be performed. For these variants functionality will be evaluated with the use of transfected cells. If these studies also show DPD deficiency the variant will be classified as deleterious. All novel variants identified during sequencing will be analyzed using an in silico analysis (DPYD-varifier) as a secondary analysis to predict if a variant is deleterious. Results will be correlated with DPD enzyme activity. This is an observational study, no dose modifications will be applied.

Study burden and risks

Blood will be drawn from all participating patients for sequencing of the DPYD gene and DPD enzyme activity measured in PBMCS.

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. Pathologically confirmed malignancy for which treatment with a fluoropyrimidine is considered to be in the patient*s best interest
2. Patients need to be self-declared non-Western
3. Age * 18 years
4. Able and willing to give written informed consent;
5. WHO performance status of 0, 1 or 2
6. Life expectancy of at least 12 weeks
7. Able and willing to undergo blood sampling for study related analysis
8. Adequate baseline patient characteristics (complete blood count, hepatic function which involves serum bilirubin, AST, ALT, and renal function)

Exclusion criteria

1. Prior treatment with fluoropyrimidines
2. Patients with known substance abuse, psychotic disorders, and/or other diseases expected to interfere with study or the patient*s safety

Study design

Design

Study type: Observational invasive
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-11-2020
Enrollment:	600
Type:	Actual

Ethics review

Approved WMO

Date:	04-12-2019
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	04-03-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	28-08-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	18-09-2020
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL69669.058.19

Study results

Date completed:	10-03-2022
Actual enrolment:	22