Safety, feasibility and cost-effectiveness of genotype-directed individualized dosing of fluoropyrimidines

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

Summary

ID

NL-OMON45080

Source
ToetsingOnline

Brief title
Genotype-directed individualized dosing of fluoropyrimidines (M14DPD)

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer (breast cancer, colorectal cancer, gastric cancer)

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Alpe d'HuZes/KWF-fonds;ademtest wordt gefinancierd door Cambridge Isotope Laboratories Inc;Andover;MA;USA,Cambridge Isotope

Laboratories Inc, Andover, MA, USA

Intervention

Keyword: 5-fluorouracil, capecitabine, dihydropyrimidine dehydrogenase, genotyping

Outcome measures

Primary outcome

The primary endpoint in this study is the incidence of severe treatment-related toxicity (CTC grade 3 to 5) in patients carrying DPYD variants compared to wild type patients.

Secondary outcome

Secondary endpoints are: cost-effectiveness, assessment of pharmacokinetics and DPD enzyme activity.

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. Upfront genotype-directed dose-adaptation is technically and logistically feasible, but has not been uniformly implemented as standard of care since improvement of patient safety and cost-effectiveness of the approach have been studied insufficiently. Upfront phenotype-directed dosing has not been routinely implemented yet in clinical practice either, due to insufficient evidence on clinical validity and utility, bio-analytical issues, logistical and financial issues. In this study it will be investigated whether genotype-and phenotype-directed dosing of fluoropyrimidines improves patient safety. It is expected that tailoring fluoropyrimidine therapy to the patient*s genotype and phenotype improves safety and reduces the costs of treatment of early and advanced breast,

colorectal and gastric cancer by reducing severe treatment-related toxicity and should thus change the standard of care.

Study objective

The primary objective is to determine whether the rate of severe toxicity (CTC grade 3 to 5) associated with fluoropyrimidine treatment can be significantly diminished by individualized dosing of fluoropyrimidines based on upfront genotypic assessment of DPD deficiency.

Secondary objectives are:
• To determine whether individualized dosing based on upfront genotypic assessment of DPD deficiency is cost-effective.
• To determine the additional value of an array-based screening of additional decreased activity DPYD-alleles, by determining associations between these variants and occurrence of severe fluoropyrimidine-induced toxicity.
• To assess the pharmacokinetic profile of capecitabine and 5-FU in DPD deficient patients (e.g. patients carrying variant DPYD alleles) given reduced dosages of the respective drugs.
• To determine the clinical sensitivity, specificity, positive predictive value and negative predictive value of phenotype-based screening using the endogenous DHU/U ratio.
• To determine the clinical sensitivity, specificity, positive predictive value and negative predictive value of phenotype-based screening using the uracil test dose.
• To determine the clinical sensitivity, specificity, positive predictive value and negative predictive value of phenotype-based screening using the uracil breath test.

Study design

The study will have a duration of about 24 months. A number of 1250 patients will be included. In this study prospective screening for four single nucleotide polymorphisms (SNPs) in DPYD (DPYD*2A, c.2846A>T, c.1236G>A/HapB3 and DPYD*13) will be performed using validated real-time polymerase chain reaction (PCR) assays. Patients with a SNP in DPYD will be treated with a 25-50% reduced starting dose, depending on which SNP is identified. The dose will be titrated in subsequent cycles, to achieve maximal safe exposure. In addition to the genotyping, the DPD phenotype of all patients will be determined by measuring the baseline dihydrouracil/uracil (DHU/U) ratio, in order to investigate whether phenotype-guided treatment can further improve patient safety. In a subgroup of patients, other phenotyping methods will be tested: measuring the plasma levels of uracil after an uracil test dose and a uracil breath test after a dose of [2-13C] -labeled uracil. To validate these tests, these phenotyping results will be compared with the results of a DPD activity assay (which measures DPD enzyme activity in peripheral blood

mononuclear cells), which is considered the gold standard in measuring the DPD phenotype. The results of the phenotyping tests will be evaluated at the end of this study and will be the basis for a subsequent study. In this next study the combined use of upfront genotype- and phenotype based DPD-screening will be investigated. Patients will be followed for toxicity during the whole treatment period. The cost-effectiveness of genotype-guided dosing will be calculated.

Intervention

The intervention will consist of dose adjusting for fluoropyrimidines for patients heterozygous for a polymorphism in DPD. The degree of dose adjustment is depending on the SNP that is found. For DPYD*2A and DPYD*13 the dose will be 50% of standard dose and for c.2846A>T and c.1236G>A/HapB3 the dose will be 25% lowered.

Study burden and risks

Blood will be drawn from all participating patients for determining the genotype and the DHU/U ratio, prior to start of the fluoropyrimidine therapy. Pharmacokinetic analyses will be performed on a subgroup of the participating patients (all patients carrying a SNP in DPYD), for which hospitalization for the duration of 9 hours is necessary and blood samples at 9 (for capecitabine and 5-FU bolus injection) or 11 (for 5-FU continuous infusion) different time points will be collected. In a subgroup of 15 patients the endogenous DHU/U ratio at different time points will be determined. Blood samples will be drawn at 9 time points and hospitalization for the duration of 9 hours is necessary. The uracil test dose assay and the breath test will be performed on a subgroup of the participating patients (around 260 patients). For the uracil test dose assay patients will have to swallow an uracil suspension, hospitalization during 3 hours is necessary and blood samples at 2 different time points will be collected. For the uracil breath test patients have to swallow an aqueous solution of [2-13C]-uracil and exhaled breath samples and blood samples are collected (hospitalization of around 1 hour is necessary). One extra bloodsample for these patients undergoing these two phenotyping tests is necessary to determine the DPD enzyme activity.
Since dosages will be reduced for patients carrying a SNP in DPYD there will be a small risk of underdosing for these patients. This risk will be very small, since dose escalation according to tolerance after the first two courses will be performed.

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. WHO performance status of 0, 1 or 2
3. Life expectancy of at least 12 weeks
4. Able to swallow and retain oral medication
5. Able and willing to undergo blood sampling for pharmacogenetic and phenotyping analysis;For subgroup only:
6. Able and willing to undergo blood sampling and breath sampling at several time points
7. Able and willing to receive uracil for the test dose assay
8. Able and willing to receive [2-13C] -labeled uracil for the breath test

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
3. Women who are pregnant or breast feeding

4. Both men and women who refuse to use reliable contraceptive methods throughout the study
5. Patients with a homozygous polymorphic genotype or compound heterozygous genotype for DPYD.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	30-04-2015
Enrollment:	1250
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	fluorouracil
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	18-12-2014

Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-02-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-05-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-07-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	19-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-01-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2014-005064-15-NL
ClinicalTrials.gov	NCT02324452
CCMO	NL51410.031.14