

PHARMACOGENOMIC AND PHARMACOKINETIC SAFETY AND COST-SAVING ANALYSIS IN PATIENTS TREATED WITH FLUOROPYRIMIDINES

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Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON33759

Source

ToetsingOnline

Brief title

Pharmacogenomic guided dosing of fluoropyrimidines

Condition

- Other condition
- Malignant and unspecified neoplasms gastrointestinal NEC
- Purine and pyrimidine metabolism disorders

Synonym

DPD-deficiency, metabolism disorder

Health condition

mammarcarcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: Ministerie van OC&W, subsidie aanvraag nog in te dienen (bij ZonMW)

Intervention

Keyword: Dihydropyrimidine dehydrogenase, DPD-deficiency, DPYD*2A, Pharmacogenomics

Outcome measures

Primary outcome

Primary outcome parameter is safety of the treatment of DPYD*2A mutant patients with capecitabine or 5-FU. Toxicity outcome will be monitored according to NCI-CTC.

Secondary outcome

Secondary outcome parameters are:

- costs, to determine whether this strategy is cost-saving, which will be assessed by an incremental cost-effectiveness analysis.
- to assess an individual treatment algorithm for DPYD*2A mutant patients for capecitabine and 5-FU.
- to determine the pharmacokinetic parameters of capecitabine and 5-FU in DPYD*2A mutant patients.
- to perform a DPD-activity measurement in patients with the DPYD*2A mutation
- assessment of the toxicity in wild type patients for DPYD*2A, who have been prospectively screened prior to start of therapy and did actually receive a treatment with fluoropyrimidine drugs, by investigation of the patient files

- statusonderzoek naar toxiciteit in wild type patienten voor DPYD*2A, die in het kader van deze studie voorafgaand de therapie gegenotypeerd zijn en daadwerkelijk zijn gestart met een fluoropyrimidinebehandeling.

Study description

Background summary

Fluoropyrimidines are a group of widely prescribed anticancer agents. Although 5-FU is in clinical use for 50 years, it remains a drug with poorly predictable severe toxicity, which in some cases is fatal. An important factor for fluoropyrimidine-associated toxicity is polymorphism in dihydropyrimidine dehydrogenase (DPD), the enzyme that metabolizes 85% of 5-FU to inactive compounds.

The polymorphism IVS14+1G>A (DPYD*2A) has been shown to have a great impact on DPD-activity. Retrospectively, the DPYD*2A mutation is found in about 25% of all patients who developed severe hematological and/or gastro-intestinal toxicity after full-dose treatment with capecitabine or 5-FU.

This single nucleotide polymorphism is a point mutation, which leads to complete skipping of exon 14 during pre-mRNA splicing, resulting in a protein with absent activity. In the Netherlands DPYD*2A has a heterozygous frequency of 1.8%. It is reported that heterozygote individuals for DPYD*2A have a 50% reduction in DPD-activity, whereas in homozygotes DPD is complete deficient. The reduced or absent capacity to metabolize 5-FU by DPD, leads to a higher and longer exposure of 5-FU to the body, which in turn causes typical fluoropyrimidine (non-)hematological toxicity such as bone marrow suppression, leucopenia, diarrhea and mucositis. Prolonged periods of hospitalization of several weeks are indicated for the treatment of the toxicity.

We develop a rapid screening method for DPYD*2A, which is suitable for routine assessment prior to therapy. Other methods described in literature such as activity measurements in leucocytes or determination of the uracil / dihydrouracil ratio in urine for predicting DPD activity are time-consuming, highly variable and above all not predictive, thereby not suitable for clinical practise. There is an unmet need for other methods for predicting DPD-deficiency.

The aim is to demonstrate that total number and degree of toxicity, and related costs for the treatment of the toxicity, can be prevented by adaptive dosing in DPYD*2A mutant individuals.

Study objective

The primary objective of the study is to prospectively determine whether

fluoropyrimidine-induced toxicity is preventable by dose adjustment prior to start of the first administration based on the polymorphic status of the DPYD*2A polymorphism in DPYD, in comparison with retrospectively determined full-dose treated heterozygous patients and to determine whether this strategy is cost-saving.

Secondary objectives of the study are to validate an individualized treatment algorithm for capecitabine and 5-FU therapy based on the polymorphic status of DPYD*2A and to assess the pharmacokinetic profile of capecitabine and 5-FU in DPYD*2A mutants given reduced dosages of the respective drugs.

Study design

Prospective, clinical, non-randomized, pharmacogenetic, -kinetic and *economic non-randomized safety analysis in patients treated with capecitabine or 5-FU.

Intervention

The polymorphic status of DPYD*2A will be assessed prospectively, prior to fluoropyrimidine treatment. Wild-type patients will drop out of the study after determination. Hetero- and homozygous mutant patients are given a dose reduction of at least 50% and 85%, respectively. If the first 2 cycles are fully completed and considered safe, doses may be increased in subsequent cycles.

Further dose reductions may be applied at any time.

Study burden and risks

4 ml of blood will be obtained prior to start of therapy for the assessment of DPYD*2A status. In DPYD*2A mutant patients a maximum of 12 plasma samples (8 ml blood / sample) will be obtained on day 1 of course number 1. This will require only one extra venapuncture for the whole blood sampling procedure on that day. If patients receive a dose modification in any further cycle, the same blood sampling procedure will be performed on day one of the respective course. Any risk hereby is negligible.

Contacts

Public

Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
1066 CX Amsterdam
NL

Scientific

4 - PHARMACOGENOMIC AND PHARMACOKINETIC SAFETY AND COST-SAVING ANALYSIS IN PATIENTS ...
16-06-2025

Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
1066 CX Amsterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- Patient is considered for treatment with capecitabine or 5-FU
- Age 18 years or older
- Able and willing to undergo blood sampling for pharmacogenetic and pharmacokinetic analysis
- Life expectancy more than 2 months allowing adequate follow up of toxicity evaluation and antitumor activity
- Minimal acceptable safety laboratory values
- WHO performance status of 0 - 2
- No radio- or chemotherapy within the last 3 weeks prior to study entry

Exclusion criteria

- Patients with known alcoholism, drug addiction and/or psychotic disorders in the history that are not suitable for adequate follow up.
- Women who are pregnant, breast feeding or women of childbearing potential who refuse to use a reliable contraceptive method throughout the study.

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Pending
Start date (anticipated):	01-02-2007
Enrollment:	500
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	adrucil
Generic name:	5-fluorouracil
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Xeloda
Generic name:	capecitabine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO	
Date:	19-02-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	
Date:	13-06-2007

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO	
Date:	13-07-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2007-000412-82-NL
CCMO	NL15956.031.07