

A combination of pre-screening for DPD deficiency by genotyping/phenotyping methods and pharmacokinetics-guided dosing of 5-FU for precision treatment to prevent severe toxicity in gastrointestinal cancer patients.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52496

Source

ToetsingOnline

Brief title

DPD guided 5FU precision treatment in GI cancer

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym

DPD deficiency

Research involving

Human

Sponsors and support

Primary sponsor: Isala Klinieken

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Dihydropyrimidine Dehydrogenase Deficiency, DrugMonitoring, Fluorouracil, Genetic Association Studies

Outcome measures

Primary outcome

The primary outcome of the study is the clearance of 5-FU at steady state (Clss) measured in ml/min. Among cancer patients treated with 5-FU, we will compare the variation in clearance between the four common DPYD variant allele carriers and DPYD wild-type carriers.

Secondary outcome

The secondary study parameters are the incidence of 5-FU related toxicities, U/DHU ratio, DPD phenotype (EM, IM, and PM), 5-FU doses, dosage adjustment and time to reach target AUC (cycle number).

Study description

Background summary

Fluorouracil (5-FU) are broadly used in chemotherapeutic regimens for the treatment of cancers. Dihydropyrimidine dehydrogenase (DPD) is a major enzyme in the 5-FU metabolism pathway. Patients with a partial or complete DPD deficiency have a strongly reduced capacity to metabolize 5-FU which may result in severe or life-threatening toxicity when treated with a standard dose of fluoropyrimidines. A partial DPD deficiency is present in 3-5% of the North American and European population. DPD deficiency is most often caused by genetic variants in the gene encoding DPD (DPYD). The four DPYD variants

considered most clinically relevant and with statistically significant association with severe toxicity are DPYD*2A (rs3918290, c.1905+1G>A, IVS14+1G>A), c.2846A>T (rs67376798, D949V), c.1679T>G (rs55886062, DPYD*13, I560S), and c.1236G>A (rs56038477, E412E, in haplotype B3). Prospective testing for DPD deficiency can prevent severe toxicity or mortality. Several methods have been proposed for detection of DPD deficiency, based on either genotyping of DPYD or measurement of the DPD phenotype. However, DPD deficiency is not the only factor associated with variable concentrations of 5-FU. 5-FU displays an exposure-response relationship between systemic exposure and clinical events. Therapeutic Drug Monitoring (TDM) or pharmacokinetics (PK)-guided dosing of 5-FU is also considered as an alternative to ensure an acceptable exposure of 5-FU. Upfront DPD screening combined with PK guided 5-FU dosing as a tool to personalize treatment has never been studied before. In this study, we aim to investigate the PK of 5-FU for the 4 most common DPYD genetic variants, in order to better define a safe starting dose for 5-FU in DPD deficient patients.

Study objective

The primary objective of this study is to investigate the clearance of 5-FU for the 4 most common DPYD gene variants compared to the clearance of 5-FU in DPYD wild-type patients. The secondary objectives of this study are to determine the toxicity incidence and the extent of DPD deficiency as measured by Uracil Loading Test (ULT) for the 4 most common DPYD variants, to evaluate the safety and tolerability of reduced starting dose of 5-FU in patients with DPD deficiency, to demonstrate the ability to achieve a target AUC range, to establish that PK-guided 5-FU dosing decreases the incidence of 5-FU related toxicities, to establish the sensitivity, specificity and predictive values of the DPYD genotyping test and .to optimize the sampling moment of 5-FU in order to minimize patient discomfort related to TDM procedures

Study design

The study is designed as a single-centre prospective inception cohort study. All patients will be screened for DPD deficiency by DPYD genotyping and separated into two groups; DPYD common variants and control group. Patients with DPYD wild-type but who experience CTC grade 3-4 toxicity will also be included in this study as a toxicity group. Patients will be tested with an oral ULT to identify their DPD phenotype and measured an endogenous U/DHU ratio. Therapeutic drug monitoring will be performed to follow-up patients* 5-FU plasma concentration after start chemotherapy treatment. 5-FU plasma concentrations will be monitored until a steady state AUC of 20-30 mg.h/L is reached or maximum 4 treatment cycles is reached.

Intervention

5-FU dose adaptation according to the IATDMCT guideline.

Study burden and risks

The burden associated with participation:

Patients have to participate in this study for maximum 5 study visits.

Pre-screening: Physical examination and DPYD genotyping (1 blood sample (3 mL))

Visit ULT*: ULT + endogenous U/DHU ratio (3 blood samples, total 9 mL)

Visit 1**: 5-FU TDM (1 blood sample 3 mL; in PK subgroup in total 4 samples of 3 mL)

Visit 2**: 5-FU TDM (1 blood sample 3 mL; in PK subgroup in total 4 samples of 3 mL)

Visit 3***: 5-FU TDM (1 blood sample 3 mL)

Visit 4***: 5-FU TDM (1 blood sample 3 mL)

* The ULT can be performed any time during the study, provided that there is at least a 48 hr interval between the test and the previous or next chemotherapy administration.

** A subgroup of 8-12 patients will be subject to additional blood sampling on day 1 and day 2 of the first 2 treatment cycles. Three extra blood samples will be drawn during continuous infusion of 5-FU.

*** As long as the target AUC has not yet been reached

The risk-benefit analysis:

The possible risks of this study are related to standard risk of venapunctures and mild adverse reactions that might occur after uracil consumption during the ULT procedure. The risk associated with extra blood sampling is minimal. The results of the measurements will be used to individualise the chemotherapy dose and add to improved patient safety.

Group relatedness:

5-FU based chemotherapy regimens are the first-line therapy for gastrointestinal cancer patients. Therefore, this group of patients is related to this study.

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

- age 18 years and older
- histological proof of gastro-intestinal cancer
- patient is considered for treatment with capecitabine or 5-FU
- acceptable safety laboratory values
- ECOG performance status 0-2
- able and willing to give written informed consent
- able and willing to undergo blood sampling for DPYD genotyping, DPD phenotyping and pharmacokinetic analysis

Exclusion criteria

- symptomatic or uncontrolled central nervous system metastases
- patient who cannot submit itself to the formal follow-up for psychological, social, family or geographical reasons
- women who are pregnant or breast-feeding
- women not consenting to use adequate contraceptive precautions during the study
- significant serious pathology or any instable medical condition (cardiac pathology uncontrolled, myocardial infarction within 6 months before enrolment, systemic active uncontrolled infection, cirrhosis (Child-Pugh score C), renal failure (GFR < 20 ml/min))

- any investigational agent within 4 weeks before enrolment
- cimetidine or sorivudine use (due to drug-drug interactions with 5-fluorouracil and capecitabine)

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL	
Recruitment status:	Recruiting
Start date (anticipated):	01-01-2020
Enrollment:	75
Type:	Actual

Ethics review

Approved WMO	
Date:	05-11-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	
Date:	20-02-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	
Date:	19-05-2022
Application type:	Amendment

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	NL70778.075.19