Correlation between endogenous DPD substrate concentrations and the pharmacokinetics and toxicity of 5-fluorouracil in patients with colorectal or pancreas cancer

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Primary objective: To determine the correlation between the baseline endogenous DPD substrate plasma ratios of DHU/U and DHT/T with the pharmacokinetics of 5-FU in patients with pancreas or colorectal cancer treated with intravenous 5-FU-based...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal neoplasms malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON48600

Source
ToetsingOnline

Brief title
FUUT

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
Colon cancer, colorectalcarcinoma; pancreas cancer, pancreascarcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: Catharina ziekenhuis en potentieel catharina onderzoeksfonds

Intervention

Keyword: 5-Fluorouracil, dihydropyrimidine dehydrogenase, thymine, uracil

Outcome measures

Primary outcome

The primary endpoint of the study are the plasma concentrations of 5-FU, DHFU and endogenous biomarkers U, DHU, T and DHT at all time points by using LC-MS/MS.

Secondary outcome

- Ratios of DHU/U, DHT/T and DHFU/FU will be calculated by using the plasma concentration

- Determine DPYD genotype for each patient. If applicable, additional SNP analysis within the DPYD gene will be conducted at study end

- DPD enzym activity

- Severe adverse events following 5-FU infusion, including:

* Toxicity-related hospitalization

* Change in dose intensity: prolonged interval or dose reduction

* Myelosuppression (leukocytes, neutrophils and thrombocytes) grade *3 according to CTC-AE criteria

* Other toxicities including grade *3 mucositis and diarrhoea according to the CTC-AE criteria

Study description

Background summary

The anticancer drug 5-fluorouracil (5-FU) is widely used in the treatment of amongst others early and advanced colorectal, gastric, pancreas and breast cancer. 5-FU is mainly metabolized by the enzyme dihydropyrimidine dehydrogenase (DPD), an enzyme encoded by the DPYD gene. Genetic polymorphism in this gene may lead to DPD deficiency and thereby an increased risk of drug-induced severe toxicity. In the Caucasian population, 3 to 5% has a partial DPD-deficiency and 0.1 to 0.2% has a complete deficiency.(1,2) DPD deficiency can lead to severe toxicity (grade 3 to 5, according to CTC-AE version 4.03), such as myelosuppression, mucositis, diarrhoea and hand-foot syndrome. Measuring the DPYD genotype prior 5-FU-based chemotherapy has shown to be able to prevent drug-induced severe toxicity of 5-FU. The clinical utility has thus far been demonstrated for four polymorphisms, i.e. DPYD*2A; *13; 2846A>T; 1236G>A, which are therefore routinely determined prior to start of chemotherapy. Despite the use of genotyping, a significant proportion of patients still develop 5-FU-related severe toxicity. Since both endogenous uracil (U) and thymine (T) are being converted by DPD into dihydrouracil (DHU) and dihydrothymine (DHT), respectively, patients with a low DHU/U and/or a low DHT/T plasma ratio before start of 5-FU based therapy have higher risk of 5-FU induced severe toxicity. It is not known what the correlation of the DHU/U and/or DHT/T plasma ratios is compared to the actual DPD enzyme activity within the white blood cells. The DPD enzyme activity will not only be compared to the plasma ratios DHU/U and/or DHT/T but also to pharmacokinetics of 5-FU. As the DPD enzyme activity test is a more time consuming, labour intense, complex and expensive test to perform, the use of endogenous biomarkers such as uracil and thymine might favour over the DPD enzyme activity test.
In this study we will investigate the correlation between the endogenous DPD substrates uracil and thymine as well as the DPD enzyme activity with the pharmacokinetics and toxicity of 5-FU in patients with colorectal or pancreas cancer treated with prolonged infusions of 5-FU. The ultimate goal is to develop an easy to measure additional predictive marker besides DPYD genotype in order to prevent 5-FU induced severe toxicity.

Study objective

Primary objective:
To determine the correlation between the baseline endogenous DPD substrate plasma ratios of DHU/U and DHT/T with the pharmacokinetics of 5-FU in patients with pancreas or colorectal cancer treated with intravenous 5-FU-based chemotherapy.

Secondary objectives:

- To determine the potential changes in U, DHU, T and DHT concentrations over time during the prolonged 5-FU infusion
- To determine the DHU/U, DHT/T and DHFU/FU ratios over time during 5-FU prolonged infusion
- To establish a cut-off concentration in a daily Dutch patient population for all measured analytes, their metabolites and ratios, including 5-FU, DHFU, U, DHU, T and DHT
- To determine the effect of DPYD genotype on the U, DHU, T and DHT concentrations and on the pharmacokinetics of 5-FU
- To determine the correlation between serious adverse events or 5-FU toxicity to AUC of 5-FU, DHU/U or DHT/T ratio or DPD enzyme activity
- To determine the effect of other genetic polymorphisms on the pharmacokinetics of 5-FU (if applicable)
- To determine the correlation between the DPD enzyme activity and the DHU/U, DHT/T of DHFU/FU plasma ratios, and 5-FU pharmacokinetics.

Study design

Prospective, non-randomized, pharmacokinetic study

Study burden and risks

To determine the DPD enzyme activity a sample of 12mL whole blood (2x 6mL EDTA) is obtained after connecting the port-a-cath. Since connecting the port-a-cath is needed to administer the chemotherapy there is no need for a puncture.
At t=0, prior starting the 5-FU infusion, 4mL of whole blood (EDTA tube) is obtained by using a venflon. This sample is used to determine the concentrations of uracil, DHU, T and DHT.
During treatment the samples at t=0.5 and 2 hours are retracted by the same venflon so there is no need for another puncture. The sample at t=44 hours is taken by the port-a-cath, this way another puncture is not needed. At each time point during treatment 8mL of whole blood (2x 4mL EDTA) will be retracted to determine the concentrations of uracil, DHU, T, DHT, 5-FU and DHFU.
The risk of drawing blood from a vein include discomfort at the site of puncture and possible redness and swelling around the puncture site. Since the prolonged 5-FU infusion is routinely administered within the hospital the intervention does not require additional or prolonged hospital visits.

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 5-FU is indicated in the FOLFOX, FOLFIRI or FOLFIRINOX regimen.
2) Minimal acceptable safety laboratory values defined as
a. ANC of * 1.5 x 109 /L
b. Platelet count of * 100 x 109 /L
c. Hepatic function as defined by serum bilirubin * 1.5 x ULN, ALAT and ASAT * 2.5 x ULN; in case of liver metastases ALAT and ASAT * 5 x ULN.
d. renal function as defined by MDRD >30 ml/min

Exclusion criteria

1. Patients with known substance abuse, psychotic disorders, and/or other diseases expected to interfere with study or the patient*s safety
2. Women who are pregnant or breast feeding
3. Patients in whom the bolus injection will be skipped due to e.g. toxicity of previous chemo therapy regimen.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-07-2019
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	16-04-2019
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-11-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL67140.100.18