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

No registrations found.

Ethical review	Positive opinion
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON21471

Source
NTR

Brief title
FUUT

Health condition

Colorectal or pancreas cancer

Sponsors and support

Primary sponsor: Catharina Hospital Eindhoven
Source(s) of monetary or material Support: Catharina Hospital Eindhoven

Intervention

Outcome measures

Primary outcome

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 outcome

- 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
- To determine the effect of other genetic polymorphisms on the pharmacokinetics of 5-FU (if applicable)

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. In this study we will investigate the correlation between the endogenous DPD substrates uracil and thymine 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

A low ratio of U/DHU and/or T/DHT can cause serious adverse events in patients treated with 5-FU continous infusion.

Study design

T= 0, 1/2, 2 and 46 hours.

Contacts

Public
Catharina ziekenhuis
M.A. Hanrath

0402399111
Scientific
Catharina ziekenhuis
M.A. Hanrath

0402399111

Eligibility criteria

Inclusion criteria

1. Pathologically confirmed malignancy for which treatment with 5-FU is indicated in the FOLFOX, FOLFIRI or FOLFIRINOX regimen.
2. Age ≥ 18 years
3. Able and willing to give written informed consent
4. WHO performance status 0-2
5. 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 non invasive
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-03-2019
Enrollment:	50
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	19-02-2019
Application type:	First submission

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
NTR-new	NL7539
Other	MEC-U : R19.002/FUUT

Study results