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

Gepubliceerd: 19-02-2019 Laatst bijgewerkt: 13-12-2022

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

Ethische beoordeling	Positief advies
Status	Werving nog niet gestart
Type aandoening	-
Onderzoekstype	Observationeel onderzoek, zonder invasieve metingen

Samenvatting

ID

NL-OMON21471

Bron
NTR

Verkorte titel
FUUT

Aandoening

Colorectal or pancreas cancer

Ondersteuning

Primaire sponsor: Catharina Hospital Eindhoven
Overige ondersteuning: Catharina Hospital Eindhoven

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

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.

Toelichting onderzoek

Achtergrond van het onderzoek

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.

Doel van het onderzoek

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

Onderzoeksopzet

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

Contactpersonen

Publiek

Catharina ziekenhuis
M.A. Hanrath

0402399111

Wetenschappelijk

Catharina ziekenhuis
M.A. Hanrath

0402399111

Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

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

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

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.

Onderzoeksopzet

Opzet

Type:	Observationeel onderzoek, zonder invasieve metingen
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving nog niet gestart
(Verwachte) startdatum:	01-03-2019
Aantal proefpersonen:	50
Type:	Verwachte startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies

Datum:	19-02-2019
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL7539
Ander register	MEC-U : R19.002/FUUT

Resultaten