Personalized prediction and regulation of 5-FU exposure

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Primary objective:To determine the percentage of the patients that achieve optimal 5-FU exposure within two dose cycles of 5-FU, which is defined by an AUC target of 5-FU between 20 and 30 mg h/L or dose limiting toxicity.Secondary objectives:-To...

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

Summary

ID

NL-OMON54497

Source
ToetsingOnline

Brief title
PERFU

Condition

- Gastrointestinal neoplasms malignant and unspecified

Synonym
intestinal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Voorlopig eigen financiering;subsidie wordt aangevraagd.

Intervention

Keyword: 5-FU, fluorouracil, PERFU, TDM

Outcome measures

Primary outcome

The percentage of the patients that achieve optimal 5-FU exposure within two dose cycles of 5-FU, which is defined by an AUC target of 5-FU between 20 and 30 mg h/L or dose limiting toxicity.

Secondary outcome

Secondary endpoints of this study are: the minimum amount of blood sample required to safely adjust 5-FU dosing in our routine clinical practice, AUC contribution of 5-FU bolus infusion in PK model versus simple formula (Css x t), frequency of AEs below, within and above target window, intra-individual variation in 5-FU AUC, correlation DPD activity with 5-FU exposure and toxicity and the correlation between AEs and total 5-FU exposure.

Study description

Background summary

It is widely well-known that 5-FU dosing based on body surface area (BSA) is associated with wide variations of 5-FU systemic exposure and 5-FU toxicity. Beumer et al. summarized previous clinical studies of 5-FU and observed approximately 40% inter-individual variability in 5-FU exposure in these studies. Furthermore, only 25% of the patients are within the therapeutic window and 60% of the patients are underdosed after the first cycle. Recently, Beumer et al. presented a strong case for 5-FU dose adjustment based on 5-FU plasma concentrations, so called Therapeutic Drug Monitoring (TDM), in order to reduce inter-individual variability in 5-FU exposure and toxicity, while preserving efficacy. Despite sufficient evidence on the efficacy of TDM of 5-FU to reduce toxicity, while maintaining the efficacy of treatment in patients, several problems such as technical handling of blood samples, accurate

measurements, calculation of 5-FU exposure and 5-FU dosing advice need to be clarified before introducing TDM of 5-FU in standard routine clinical care. Therefore the aim of this study is to validate whether TDM of 5-FU is an effective tool to regulate individual 5-FU exposure in both Amsterdam UMCs.

Study objective

Primary objective:
To determine the percentage of the patients that achieve optimal 5-FU exposure within two dose cycles of 5-FU, which is defined by an AUC target of 5-FU between 20 and 30 mg h/L or dose limiting toxicity.

Secondary objectives:
-To determine whether minimal sampling of 5-FU blood samples is sufficient to safely adjust 5-FU dosing in our routine clinical practice.
-To develop 5-FU PK model for our Amsterdam UMC 5-FU patients using NONMEM statistics.
-To investigate the contribution of bolus 5-FU exposure in PK model as compared to the exposure calculations with the simple formula (Css x t).
All 5-FU exposure correlations below this point will be calculated with the simple formula as well as with PK modelling:
-To determine the frequency and severity of AEs at 5-FU exposure with below, within and above the target window,
-To determine the correlation between DPD activity with 5-FU exposure in the first 5-FU dose cycle
-To determine the intra-individual variation in 5-FU AUCs in all six 5-FU cycles.
-To investigate the correlation between AEs and the total 5-FU exposure in six dose cycles.

Exploratory objectives:
-To explore the utility of DPD-phenotyping in predicting the exposure of the first dose of 5-FU.
-Searching for new predictors in DPYD DNA variants that contribute to increased 5-FU exposure or toxicity.

Study design

Multicentre intervention study to determine the percentage of patients that achieve optimal 5-FU exposure in the Amsterdam UMCs

Intervention

A 5-FU dosing algorithm will be applied in this study to adjust the 5-FU exposure in patients until the target window of 20-30 mg*h/L or dose limiting toxicity has been reached. All other procedures will be a part of standard

care.

Study burden and risks

The risk associated with participation in this clinical trial is low. The difference between the current procedure in standard care and this study is extra 5-FU blood sampling that is required to adjust dosages. Because patients may experience 5-FU side effects upon dose increase, a maximum dose increase of 40% per cycle is applied in this study. Dose escalation will only be applied when 5-FU toxicity is absent in patients. On the other hand, dose decrease might lead to less 5-FU toxicity in patients with high 5-FU exposure.

The study burden is additional of 10 to 15 times 4 ml blood sampling and additional 15 ml blood for DPD phenotyping in VUmc patients or 5 ml blood for DPYD genotyping in AMC patients. Five blood samples from the 1st cycle is used to develop 5-FU PK model and to calculate the exposure of 5-FU for new 5-FU dose advice for the 2nd cycle. A venflon will be introduced in the peripheral vein of the patients to reduce the burden of multiple blood sampling.

In the 2nd to 5th cycle one or two samples will be drawn by venipuncture to calculate the new 5-FU dose advice for the next cycles. The blood samples in the 6th cycle are used to complete the dataset. The second blood sample in the 2nd to the 6th cycle will only be drawn if the patient is in the hospital at the end of 5-FU continuous infusion.
The number of blood samples was designed to collect the minimum amount of blood that is required to accurately and completely calculate the AUC of 5-FU and to develop 5-FU PK model.

The benefit for the patient participating in this study is that the 5-FU exposure will be personalized to reduce potential toxicity while preserving efficacy.

When toxicity can be limited through personalized regulation of 5-FU exposure, TDM of 5-FU will be applied in our standard routine care. In the future this will benefit all patients that are treated with 5-FU based chemotherapy. After this trial, future 5-FU patients might benefit from minimal 5-FU blood sampling as this study determines the minimal number of blood samples to accurately measure and calculate 5-FU exposure.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam NL1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam NL1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient undergoing FOLFOX, FOLFIRI or FOLFIRINOX treatment.
2. Patient with age >= 18.
3. Patient is able and willing to give written informed consent.
4. Patient is able and willing to undergo extra blood sampling for 5-FU analysis.

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. Inability to perform additional blood sampling in patient.

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-02-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	5-Fluorouracil
Generic name:	5-Fluorouracil
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-11-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	09-12-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	EUCTR2019-003740-77-NL
CCMO	NL71410.029.19

Study results

Date completed: 10-07-2024

Results posted: 22-11-2024

First publication
14-06-2024