Identification of the mechanisms of 5-fluorouracil (5-FU)-induced Gastrointestinal (GI) toxicity in human colon

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON55582

Source
ToetsingOnline

Brief title
5-FU-induced toxicity in GI system

Condition

- Other condition

Synonym
diarhrea, gastrointestinal toxicity

Health condition

5-FU toxicity in the gastrointestinal system

Research involving

Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: IMI2□2015□06□0

Intervention

Keyword: 5-fluorouracil, Adverse effects, Gastrointestinal, Toxicity

Outcome measures

Primary outcome

The major outcome parameter is the observed differences in the whole genome transcriptomic responses after exposure to 5-FU in colon epithelium. These genetic markers will be further associated with markers of toxicity (citrulline and calprotectin). These outcomes in humans will give better insight on the relevance of markers identified in previous in vitro studies, and how data obtained from colonoids culture after exposure to 5-FU and assessment of 5-FU induced toxicity can be translated to humans.

Secondary outcome

Secondary outcome parameters include other molecular markers associated to 5-FU induced toxicity in the colon such as citrulline and calprotectin, which can be measured in faeces and blood. These outcomes will help to understand the mechanisms underlying 5-FU intestinal toxicity.

Study description

Background summary

One of the major complications during pharmacological treatment of patients is

the occurrence of adverse drug reactions (ADRs), for which the most affected organs are the liver, kidney, heart and the gastrointestinal-immune system. In comparison to the other organs, less progress has been made on human*relevant prediction of drug*induced intestinal toxicity, and it is clear that large data gaps are currently present. Therefore, new experimentation is required to assess GI toxicity by analyzing gene profile responses induced by exposure of GI system to different medicines. From a series of selected compounds, this study will specifically focus on 5-fluorouracil (5-FU)-induced intestinal toxicity. 5-FU was chosen as the first pharmaceutical to be studied in view of its wide use in cancer-therapy. The study will start by inclusion of metastatic breast cancer patients that will be receiving 5-FU as part of their medical treatment. These patients will receive an oral monotherapy consisting of cycles of two weeks treatment with capecitabine followed by one week without treatment. Capecitabine is a pro-drug that, after intake is converted into 5-FU, which is the actual cytostatic agent. After the first cycle, alterations in the physiology and morphology of colon biopsies will be evaluated, and 5-FU-induced transcriptomics signatures will be established through quantitative RNA sequencing. By doing so, we intend to obtain a better insight in the changes in the gene profile of biopsies caused by 5-FU as well as on its mechanism of action and toxicity. Eventually, we intend to compare this data with in vitro organoids and animal models and determine whether there is any relation or translatability between the models. The study can therefore be regarded as a validation study of potential in vitro and in vivo alternative models for studying drug induced GI-toxicity.

Study objective

In this study, the primary aim is to evaluate the influence of 5-FU exposure on the gene expression profile in human colonic biopsies from healthy tissue. In addition, morphological changes and the molecular toxicity biomarkers citrulline and calprotectin will be measured as secondary outcome in blood and faeces, respectively.

Study design

This human study will include 20 metastatic breast cancer patients presenting a healthy colon. Each participant will undergo proctoscopy without any bowel preparation before and after a 2-weeks treatment cycle with 5-FU; rectal biopsies and rectal swap will be taken by a specialised nurse. Rectal swaps will be used in further studies on the impact/influence of the microbiome on the development of GI toxicity. Additionally, patients will be asked to donate a venous blood sample for the analysis of citrulline, 5-FU and its metabolites, and a stool sample for the analysis of faecal calprotectin. Data analysis to evaluate 5-FU-induced toxicity in the colon will be performed as endpoints of the study.

Intervention

During the medical treatment, subjects will follow a sequence of two different periods: a two weeks treatment period with capecitabine followed by one week without treatment. This will be repeated during three cycles as part of their cancer therapy regimen. However, biopsy samples will be only collected after one cycle. Dose will also be adjusted according to the dihydropyrimidine-dehydrogenase (DPD) status (based on genetic testing of polymorphisms).

Study burden and risks

The burden/risk/benefit associated with participation will be as follows:

- Rectal biopsies will be taken before and after treatment with capecitabine. Biopsies will be collected during proctoscopy and therefore no specific bowel preparation is necessary. This procedure is used daily in medical practice and is a relatively safe examination method. Complications are very rare. Bleeding may occur from biopsies, but is minimal and stops quickly. If rectal bleeding persists, the patient must report it immediately;
- Rectal swaps, blood and faecal samples will be collected to one tube separately each time (one sample before and one after 2 weeks of treatment). The risks related to the collection of these samples are minimal. Rectal swaps and faecal samples are non-invasive. Blood sampling is performed by venepuncture, which is a standard procedure with low risk of bleeding;
- Genotyping for dihydropyrimidine-dehydrogenase (DPD) deficiencies prior to treatment, determined by Sanger sequencing of polymorphisms: c.1905+1G>A (*2A) in intron 14, c.1679T>G (*13) in exon 13, c.2846A>T (rs67376798) in exon 22 and c.1129-5923C>G (rs75017182) in intron 10. This is part of the standard protocol before treatment of these patients, and therefore does not add an additional burden.

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

- Metastatic breast cancer patients receiving capecitabine monotherapy as their regular first line treatment or second line treatment, which follows a first line treatment with taxanes and a recovery period of 3 weeks;
- Triple-negative breast cancer patients, whose treatment consists of standard chemotherapy with taxanes, cyclophosphamide and anthracyclines, followed by surgery, and in case a complete remission is not observed, they receive neo-adjuvant monotherapy with capecitabine;
- Advanced CRC cancer patients receiving capecitabine monotherapy as first or second line treatment, which follows a first line treatment with oxiplatin and a recovery period of at least 3 weeks;
- Age above 18 years old;
- Present with healthy colon tissue in the case of breast cancer patients.

Exclusion criteria

- Alcohol abuse up to 6 months before participation in this research, i.e. more than 4 drinks on any single day and more than 14 drinks per week for men and more than 3 drinks on any single day and more than 7 drinks per week for women;
- Patients who were under chemotherapy with capecitabine/5-FU or took any chemotherapeutical similar to capecitabine/5-FU in a period less than 6 months;
- - Current presence of any diseases related to the gastrointestinal tract, except advanced CRC cancer;;
- Current presence of symptoms related to diseases of the gastrointestinal

tract, i.e. vomiting, diarrhoea or constipation, and altered stool, such as presence of blood;
- HIV infection or hepatitis;
- Use of antibiotics and other prescribed medication and painkillers over the last 3 months (exception: paracetamol and contraceptive) and during the chemotherapy;
- Current smokers;
- Pregnant women;
- Participants of other clinical or dietary intervention studies.

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):	26-06-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO Date:	07-11-2018
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit

	Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-07-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	24-12-2019
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26903
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL65314.068.18
OMON	NL-OMON26903

Study results

Date completed:	01-12-2021
Actual enrolment:	3

Summary results
Trial ended prematurely