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

No registrations found.

Ethical review	Not applicable
Status	Pending
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON26903

Source
NTR

Brief title
5-FU-induced toxicity in GI system

Health condition

EN: Gastrointestinal, 5-fluorouracil, Adverse effects, Toxicity
NL: Gastrointestínaal, 5-fluorouracil, Schadelijke bijwerkingen, Toxiciteit

Sponsors and support

Primary sponsor: Maastricht University
Source(s) of monetary or material Support: European Committee, IMI2‐2015‐06‐0

Intervention

Outcome measures

Primary outcome

Difference in the whole genome transcriptomic response after exposure to 5-FU in colon epithelium.

Secondary outcome

Molecular markers associated to 5-FU induced toxicity in the colon such as citrulline and calprotectin.

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

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. Alterations in the physiology and morphology of colon biopsies are expected and 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.

Study design

One time before the start of the therapy and one time after 2 weeks of treatment.

Intervention

Colonic biopsy tissues will be collected before and after the treatment, after the first cycle of chemotherapy is completed. Blood and faecal samples will also be collected at that time points.

Contacts

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Eligibility criteria

Inclusion criteria

- Metastatic breast cancer patients receiving capecitabine monotherapy as their regular

treatment;

- Age above 18 years old;

- Present with healthy colon tissue

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

- Current presence of any diseases related to the gastrointestinal tract

- 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 non invasive
Intervention model:	Other

Control: N/A , unknown

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2018

Enrollment:	20
Type:	Anticipated

Ethics review

Not applicable
Application type: Not applicable

Study registrations

Followed up by the following (possibly more current) registration

ID: 55582
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL7144
NTR-old	NTR7342
CCMO	NL65314.068.18
OMON	NL-OMON55582

Study results