Systemic and local intestinal pharmacokinetics of irinotecan

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The primary objective of this study is to describe the pharmacokinetics (PK) of irinotecan, SN-38 and SN-38G in human by using apharmacokinetic compartment model .

Ethical review	Approved WMO
Status	Pending
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON56972

Source
ToetsingOnline

Brief title
TOLERATE

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Colorectal cancer, colorectal carcinoma, pancreas carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Catharina-ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Intestinal, Irinotecan, Systemic

Outcome measures

Primary outcome

The primary endpoint of the study is to describe the pharmacokinetics of

irinotecan, SN-38 and SN-38G in plasma and in theintestines by using a

pharmacokinetic compartment model

Secondary outcome

To determine the beta-glucuronidase activity in fecal samples by an

enzym-activity assay

Study description

Background summary

Irinotecan is a commonly prescribed drug for the treatment of advanced colorectal and pancreatic cancer. The metabolism of irinotecan consists of multiple steps. Irinotecan is metabolized into the active metabolite SN-38 by CES1 and CES2, present in the plasma, liver, and brain. Subsequently, SN-38 is mainly inactivated by the liver enzyme UGT1A1, which converts SN-38 into SN-38-glucuronide (SN-38G). The inactive metabolite SN-38G is excreted into the intestines via bile. Hypotheses suggest that inactive SN-38G is reactivated by bacteria that produce the enzyme called β-glucuronidase.

Various preclinical studies have investigated strategies to inhibit the intestinal bacterial metabolite β-glucuronidase. However, as far as we know, no studies have measured the concentrations of SN-38 and SN-38G in the human intestinal tract to determine whether higher intestinal concentrations correlate with higher plasma concentrations and whether higher intestinal concentrations correlate with a higher presence of β-glucuronidase-producing bacteria.

Therefore, more information about the pharmacokinetics of irinotecan in the human intestines is needed. The aim of this study is to measure the intestinal concentrations of SN-38 and SN-38G and to describe the pharmacokinetics as

comprehensively as possible using a NONMEM model. This descriptive pilot study utilizes samples from ten patients being treated with irinotecan according to standard procedure.

Study objective

The primary objective of this study is to describe the pharmacokinetics (PK) of irinotecan, SN-38 and SN-38G in human by using apharmacokinetic compartment model .

Study design

Descriptive, prospective, single centre, non-randomized pharmacokinetic pilot study

Study burden and risks

The risk associated with participation in this clinical trial is considered low.
In order to determine blood concentrations of irinotecan, a total of 16 mL (4 x 4 mL per patient) of EDTA blood will be drawn from th epatients.The first baseline blood draw is combined with the standard pre-therapy blood draw in the week before the start of chemotherapy.
The second and third blood draws are taken via a single venipuncture using a Venflon system. The blood draw at t=48h requires an additional venapuncture.There is no significant risk associated with these venapunctures, besides a small risk of thrombophlebitis, which is similar to the risk of other venapunctures performed during routine treatment of the patient.

In order to determine faecal concentrations of irinotecan, five stool samples are required. The patient collects the stool samples athome by using a standard kit. The collection of stool samples for scientific research purposes is considered as a minimally invasiveand non-burden some procedure for patients, primarily due to the inherent nature of the task. Individuals routinely engage in the natural process of defecation as part of their daily physiological functions. The stool samples will be stored in the patient*s own freezer and either handed in to at the clinician at the next visit or collected by the coordinating researcher at the patient*s home.
While stool sampling is generally considered a low-risk procedure, it is essentialto acknowledge the potential transmission of bacteria present in faecal matter, which could lead to infections. However, the risk of infection is mitigated by standard hygiene practices, which are explicitly mentioned in the enclosed manual with the stool sampling kit

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

• Pathologically confirmed malignancy for which treatment with irinotecan is indicated at a dosing regimen of >= 180 mg/m2 in 2- or 3-weekly treatment schedules.
• Patients who will start with their first cycle of treatment with chemotherapy
• Age >= 18 years
• Able and willing to give written informed consent
• Patient is able to temporarily store fecal samples in their freezer
• WHO performance status 0-2
• Minimal acceptable safety laboratory values defined as:
o ANC of >= 1.5 x 109 /L
o Platelet count of >= 100 x 109 /L
o 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.
o Renal function (eGFR) >= 50 ml/min or creatinine <= 1.5 x ULN

Exclusion criteria

• Patients with recently performed intestinal surgery including colectomy
• Patients with known substance abuse, psychotic disorders, and/or other diseases expected to interfere with study or the patient*s safety
• Patients with either a ileostomy, ascending colostomy or transverse colostomy
• Patients unable or unwilling to stop the use of (over the counter) medication or (herbal)
supplements which can interact with irinotecan (e.g. by induction of inhibition of CYP3A4)
• Patients with an inability to undergo additional blood sampling.
• Patients with an inability to collect stool samples at home (e.g. disabilities or incontinency).
• Patients with an inability to read and understand the informed consent form

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2024
Enrollment:	10
Type:	Anticipated

Ethics review

Approved WMO

Date:	26-08-2024
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL87206.058.24