Study on the effects of an OCT2/MATE1 substrate (metformin) and inhibitor (cimetidine) on the exposure of trifluridine/tipiracil (Lonsurf®) in patients with metastatic colorectal cancer (mCRC).

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON20484

Source
NTR

Brief title
SUMO

Health condition

metastatic colorectal cancer with an indication for Lonsurf treatment

Sponsors and support

Primary sponsor: Erasmus MC
Source(s) of monetary or material Support: Servier nederland farma

Intervention

Outcome measures

Primary outcome

1. To determine the possible drug interaction between Lonsurf and metformin on Lonsurf plasma pharmacokinetics (AUC) in patients with metastatic colorectal cancer.
2. To determine the possible interaction between Lonsurf and cimetidine on Lonsurf plasma pharmacokinetics (AUC) in patients with metastatic colorectal cancer.

Secondary outcome

1. To determine the possible drug interaction between Lonsurf and metformine on metformin plasma trough concentration in patients with metastatic colorectal cancer.
2. Other pharmacokinetic outcomes of both Lonsurf and metformine (i.e. clearance, maximum concentration (Cmax) and time until maximum concentration (tmax)).
3. To evaluate the incidence and severity of side-effects of treatment with Lonsurf in absence and presence of metformin and cimetidine.

Study description

Background summary

Colorectal cancer (CRC) is the third most common cancer type in men and women worldwide and even second in terms of mortality, especially in countries with a high socioeconomic development. TAS-102 (Lonsurf®; trifluridine/tipiracil), is a new antineoplastic agent and was registrated for the treatment of adult patients with metastatic colorectal cancer (mCRC). Lonsurf is comprised of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and the thymidine phosphorylase inhibitor, tipiracil hydrochloride.
Tipiracil is a substrate and inhibitor for the organic cation transporter 2 (OCT2) and the Multi-antimicrobial extrusion protein 1 (MATE1) and these transporters therefore may be involved in the elimination of tipiracil in urine. The concomitant use of a substrate and/or an inhibitor of OCT2 and MATE1 may influence tipiracil and trifluridine exposure (trifluridine exposure is correlated with tipiracil exposure) and patients may be deprived from optimal therapy.
Since OCT2/MATE1 substrates (e.g. metformin) and inhibitors (e.g. cimetidine) are often and inevitably prescribed in mCRC patients (e.g. metformin in +/- 13% of all patients) the effects on Lonsurf exposure or the possible inhibitory effect of Lonsurf on OCT2/MATE1 substrates ‘in vivo’ must be investigated to study its clinical relevance.
Therefore, the main objective of this study is to evaluate the pharmacokinetics (PK) of Lonsurf when Lonsurf is concomitantly used with metformin and cimetidine in patients with mCRC. Secondary objective is to determine the difference in metformin concentration when metformin is used with or without Lonsurf.

Study objective

Trifluridine is primarily metabolized through degradation by thymidine phosphorylase to the inactive metabolite 5-(trifluoromethyl)-uracil (FTY) without any involvement of the cytochrome P450 enzyme system. The primary route of excretion of trifluridine metabolites is renal (~55%). The renal clearance of tipiracil exceeds the glomerular filtration rate (GFR) suggesting a transporter mediated excretion of tipiracil in the urine. Tipiracil is a substrate and inhibitor for the organic cation transporter 2 (OCT2) and the Multi-antimicrobial extrusion protein 1 (MATE1) and these transporters therefore may be involved in the elimination of tipiracil in urine. The concomitant use of a substrate and/or an inhibitor of OCT2 and MATE1 may influence tipiracil and trifluridine exposure (trifluridine exposure is correlated with tipiracil exposure) as well as OCT2/MATE1 substrate exposure and patients may be deprived from optimal therapy. Therefore, the main objective of this study is to evaluate the pharmacokinetics (PK) of Lonsurf concomitantly used with metformin and cimetidine in patients with mCRC. Furthermore the influence on metformin concentrations will be determined.

Study design

Eerste inclusie oktober 2019 - laatste inclusie gepland eind 2021

Intervention

Patients treated with Lonsurf will be treated with metformin and cimetidine for 7 and 5 consecutive days respectively.

Contacts

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Eligibility criteria

Inclusion criteria

1. Age ≥ 18 years
2. Patients with a confirmed diagnosis of metastatic colorectal cancer with an indication for Lonsurf treatment.
3. WHO performance ≤ 1 (see appendix B).
4. Able and willing to sign the Informed Consent Form prior to screening evaluations
5. No concurrent medication or supplements which can interact with either Lonsurf, metformin or cimetidine during the study period (e.g. strong OCT2 or MATE1 inhibitors). (see Appendix C)
6. Abstain from grapefruit, grapefruit juice, herbal dietary supplements, acidic beverages (e.g. Cola) and herbal tea during the study period
7. Adequate baseline patient characteristics (complete blood count, serum biochemistry which involves sodium, potassium, creatinine, calculation of creatinine clearance, AST, ALT, gamma glutamyltranspeptidase, lactate dehydrogenase, ALP, Total bilirubin, Albumin, glucose)
8. BMI 18-30 kg/m2

Exclusion criteria

1. Pregnant or lactating patients
2. Patients with known impaired drug absorption (e.g. gastrectomy and achlorhydria)
3. Known serious illness or medical unstable conditions that could interfere with this study requiring treatment (e.g. HIV, hepatitis, Varicella zoster or herpes zoster, organ transplants, kidney failure (GFR<60), serious liver disease (e.g. severe cirrhosis), cardiac and respiratory diseases)
4. Patient with any type of diabetes mellitus

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	Active

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	04-10-2019
Enrollment:	18
Type:	Anticipated

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion Date:	04-10-2019
Application type:	First submission

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
NTR-new	NL8067
Other	Stichting BEBO en EMC : METC 19-0560

Study results