Effects of a short-term dietary restriction regimen in cancer patients receiving irinotecan.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON43513

Source
ToetsingOnline

Brief title
Dietary restriction followed by irinotecan chemotherapy

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Vrolijk stichting

Intervention

Keyword: Cancer, Diet, Irinotecan, Restriction

Outcome measures

Primary outcome

To demonstrate a 25% reduction of the active irinotecan metabolite, SN38, in healthy liver tissue (without reducing the intra-tumoral SN38 concentration), 24-26 hours after irinotecan administration with preceding dietary restriction compared to without preceding dietary restriction.

Secondary outcome

- To determine intra-tumoral irinotecan and SN-38 concentrations with and without preceding dietary restriction.

- To determine the systemic PK parameters of irinotecan in peripheral blood with and without preceding dietary restriction.

- To determine leukocyte number with and without preceding dietary restriction

- Toxicity of irinotecan with and without preceding dietary restriction.

- Transcriptome analysis of tumor and liver to identify mechanisms responsible for increased intra-tumoral irinotecan concentrations and decreased side effects.

Study description

Background summary

Currently, more than half of the metastatic colorectal cancer (mCRC) patients do not benefit (optimally) from intravenously administered irinotecan as second line treatment. In recent preclinical studies in mice we have shown that the anti-tumor effects and survival of irinotecan can be enhanced by fasting before

irinotecan treatment. In addition, toxicity may be seriously reduced by fasting. We have shown that short-term dietary restriction (DR) and fasting are powerful means to increase acute stress resistance and also protects against acute oxidative damage in the kidney and liver. While mice are significantly protected from the side effects of irinotecan chemotherapy after 72 hours of fasting, intratumoral drug concentrations of the active irinotecan metabolite SN-38 tend to be higher.

Study objective

Primary objective is to demonstrate a 25% reduction of the active irinotecan metabolite, SN38, in healthy liver tissue in patients with mCRC or other solid tumors as a result of preceding dietary restriction five days in advance. Secondary objectives are safety and systemic and intratumoral irinotecan pharmacokinetics. Furthermore, transcriptome analysis of tumor and liver will be performed to identify mechanisms responsible for the protective effect of dietary restriction.

Study design

Open label randomized two-arm cross-over study. Patients will be admitted to our hospital for 28 hours after the start of the first and second cycle in order to perform pharmacokinetic (PK) blood withdrawal, tumor and liver biopsies. Patients will have DR for five days during one cycle and are allowed to eat normally during the other cycle. A synthetic diet containing an estimate of 30% caloric restriction and 70% protein restriction based on the daily energy requirements calculated by using indirect calorimetry is used for five days.

Intervention

Treatment with irinotecan 600mg 3-weekly with or without dietary restriction.

Study burden and risks

Patients will be exposed to irinotecan chemotherapy, which is the standard of care for mCRC and other solid tumors. It is hypothesized that the study-intervention, DR before (irinotecan chemo-)therapy, results in less side effects and a better anti-tumor activity. The burden for patients participating in this study includes 28 hours hospital admission during two cycles, additional blood withdrawal for PK analyses (during two cycles 12 x 4ml additional blood withdrawals each, 96 ml in total) and two 18 gauge (G) needle biopsies (one of healthy liver and one of liver metastasis) during two cycles (24 hours after the first cycle and 24 hours after the second cycle). Patients will eat a synthetic diet for 5 consecutive days during one cycle, and they will have to fill in a diet diary before both cycles. The number of site visits

is comparable to standard treatment with irinotecan chemotherapy, extra are two visits to dietitian and two times indirect calorimetry. The main risks anticipated are: a small bleeding risk after the liver biopsies (see appendix F), and weight loss and general discomfort due to DR.

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 colorectal cancer or other solid tumors
*Eligible for treatment with irinotecan 600 mg 3-weekly
*Age * 18 years
*BMI 20-30kg/m2
*WHO performance status 0-1
*Written informed consent

*Adequate renal function, i.e. serum creatinin < 2 x ULN and creatinin clearance > 45 mL/min
*Patients with safely accessible liver metastases and healthy liver tissue
*Adequate coagulation status (PT-INR <1.5, APTT<1.5xULN, on the day of biopsy in patients using coumarines: PT-INR<1.5, Hb>6mmol/L, trombocyten > 100x10 9)

Exclusion criteria

*Previous treatment with irinotecan within the last 6 months
*Pregnant or lactating patients; patients with reproductive potential must use a reliable method of contraception (excluding oral contraceptives), if required.
*Serious illness or medical unstable condition prohibiting adequate treatment and follow-up.
*History of bleeding disorders (such as hemophilia) or bleeding complications from biopsies, dental procedures or surgeries.
*Patients using any anti-coagulant medication which cannot be safely stopped or counteracted at the time of biopsy
*Unable or unwilling to stop the use of (over the counter) medication of (herbal) supplements which can interact with irinotecan (e.g. by induction or inhibition of CYP3A4 (see Appendix B))
*Unable or unwilling to abstain from grapefruit or grapefruit juice during the study
*Bilirubin > 1.5 x ULN, ASAT > 5x ULN, ALAT >5x ULN
*Uncontrolled hypertension, despite medical treatment
*Cows milk and/or soy allergy and/or lactose intolerance
*Patients using insulin
*Patients with hyperventilation
*Patients unable of unwilling to fill in a food diary
*Patients using oxygen and not able to stop for 30 minutes

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-06-2016
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO Date:	11-02-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-12-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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: 29351
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL55597.078.15
OMON	NL-OMON29351