The PLCRC substudy Ultra high field 7.0 Tesla MR Spectroscopy to monitor capecitabine metabolism in liver metastases - a proof of concept study

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON43450

Source
ToetsingOnline

Brief title
The PLCRC - SPECTRE study

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC

Synonym
bowel cancer, Colorectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: 7.0 Tesla MR spectroscopy, capecitabine, Liver metastasis, metabolism

Outcome measures

Primary outcome

7T MRS characteristics on (changes in) concentration of capecitabine and metabolites measured in liver metastasis during MRS examinations obtained at discretized time point(s).

Secondary outcome

Secondary endpoints include response measurements (complete response, partial response, stable disease and progressive disease) according to RECIST and detailed information on perfusion, diffusion and acidity as determined by functional MRI.

Study description

Background summary

Capecitabine, an oral prodrug of 5-flouroracil (5FU), is the most widely used chemotherapeutic agent in the treatment of metastatic colorectal cancer. Response evaluation takes place nine weeks after start of treatment. This results in unnecessary toxicity and costs for non-responding patients, emphasizing the need to identify new markers that predict treatment response in early stage.
In the search for predictive markers, 5FU drug trapping in tumor has been correlated with tumor response. Capecitabine is developed to activate 5FU preferentially in tumor, challenging the assessment of 5FU drug trapping (non-invasively) and its use as a predictive marker in clinical practice. With 19F Magnetic resonance spectroscopy (19F MRS) it is possible to non-invasively monitor the metabolism of fluorinated drugs at specific locations in the human body. For capecitabine, previous pilot studies at 1.5 Tesla (T) and 3T showed that it was possible to detect most of its metabolites in vivo. However,

further research in humans was hampered due to low sensitivity for metabolite detection, difficulty of timing the MRS examinations due to inter-patient variation in absorption and metabolism time and the use of RF surface coils limiting spatial coverage. Recently ultra-high field 7.0 Tesla MRI has become available for clinical research. By combining high field strength and multiple coil elements, sensitivity and spatial coverage for the detection of capecitabine metabolites is increased. With 7T 19F MRS it should be possible to assess 5FU drug trapping in tumor by measuring changes in concentration of capecitabine metabolites and calculate the retained fraction of 5FU. Furthermore, by assessing 5FU drug trapping it should be possible to predict efficacy of capecitabine therapy during early treatment in individual colorectal cancer patients.

Study objective

The primary objective of this feasibility/pilot study is to find the correct scanning protocol to assess 5FU drug trapping in colorectal cancer liver metastases using 7T MRS (phase 1). Secondary objectives will be assessed during phase 2 of this study and include applying the developed scanning protocol to explore the correlation between 5FU drug trapping in liver metastasis to the efficacy of treatment according to the Response Evaluation Criteria In Solid Tumors (RECIST) and to explore whether metabolite levels correlate to perfusion, diffusion and acidity as determined by functional MRI. When both phases of this study are completed, the results of this study will be used to assess feasibility on a large continuing study investigating the correlation between 5FU drug trapping and treatment efficacy using 7T MRS and if indeed feasible, to perform sample size calculations.

Study design

This PLCRC sub-study is a proof of concept study in two phases. During phase 1 of this study we will include two times three patients to assess the optimal time points for the accurate assessment of 5FU drug trapping. MRS examinations for all patients will take place at day 14 during the first cycle of capecitabine and bevacizumab. The proxy for 5FU drug trapping in metastasis is the concentration of capecitabine or the precursor metabolite DFUR (input) divided by the concentration of the breakdown products FBAL or FUPA (ineffective output). In case DFUR and FUPA (shortest time in pharmacokinetics) can be detected in one timepoint in 3 patients of phase 1, phase 2 of this study will continue with a scanprotocol with one scan time point per patient. Else, two time points will be selected based on maximizing sensitivity in detecting capecitabine + DFUR and FBAL + FUPA. During phase 2 we will apply the developed scan protocol in another 20 patients to serve the secondary objectives. Phase 2 will be completed when all patients have received their routine CT scan for treatment evaluation after completing three cycles of capecitabine and bevacizumab.

Study burden and risks

Participating in this study will include one site visit at day 14 after start of treatment for all included patients. During this visit patients will be asked to undergo either one to three MRS examinations depending on the phase of the study patients were included in. The total scan time for each of the three scan sessions will be 30-35 minutes. To the best of our knowledge there are no short- or long term risks involved in having an MRI or MRS scan.

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

-18 years or older.

-Patients with liver metastases measurable according to RECIST in metastatic colorectal cancer.
-Patients that are planned to start with capecitabine and bevacizumab treatment as determined according to Dutch guidelines.
-Informed consent for longitudinal data collection according to the PLCRC study protocol.

Exclusion criteria

• Patients receiving triple chemotherapy for mCRC.
• Patients that received or currently receive any other kind of systemic therapy for cancer.
• Patients that received any prior radiotherapy or surgery in the liver.
• Patients with a dihydropyrimindine dehydrogenase (DPD) deficiency (heterozygous or homozygous).
• Contra-indications to MRI scanning according to hospitals 7T MRI screening guideline of the UMCU.
• Patients with severe liver dysfunction.
• Patients with a life expectancy of < 3 months.
• Pregnant or lactating women.
• Claustrofobia.
Exclusion criteria phase 2
• Patients that withdraw treatment with capecitabine and bevacizumab within the first three cycli.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	26
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	capecitabine
Generic name:	capecitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	10-03-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-05-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-06-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-06-2016
Application type:	Amendment
Review commission:	METC NedMec

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
EudraCT	EUCTR2016-000092-24-NL
CCMO	NL56286.041.16