Cholangiocarcinoma detection using an intraOperative FlUorescence Image Guided Approach with Bevacizumab-IRDye 800CW

Published: 30-04-2018
Last updated: 11-04-2024

PrimairyTo assess whether bevacizumab-800CW allows for intraoperative fluorescence imaging of perihilar cholangiocarcinoma and what dose provides the best visualization of tumor tissue by determining the tumor-to-background (TBR) ratio ex...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and biliary neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON46827

Source
ToetsingOnline

Brief title
COUGAR

Condition

- Hepatic and biliary neoplasms benign

Synonym
bile duct cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Surgvision BV,unrestricted grant van Surgvision

Intervention

Keyword: Cholangiocarcinoma, Fluorescence

Outcome measures

Primary outcome

- Standard histopathological examination to confirm higher fluorescent signals in tumour tissue compared to normal tissue.

- Calculating target to background ratios in fluorescence images obtained during and directly after the surgical procedure and fluorescence images obtained during ex vivo analyses in bread loaf slices and in histological slices (odyssey scanner, fluorescence microscopy).

- Determining the tracer distribution at microscopic level using needle based confocal laser endomicroscopy during ex vivo off table imaging.

- Measuring fluorescent signal using spectroscopy to correct for scattering.

Secondary outcome

- Intraoperative assessment of positive margins based on fluorescent images.

- Off table imaging of surgical specimen directly after excision to identify positive margins, lymph nodes and metastases based on ex vivo fluorescent images.

- Back table imaging of surgical specimen after excision to identify tumour tissue by NIR endoscopy based on ex vivo fluorescent images .

Study description

Background summary

There is a need for better visualization of tumour tissue, lymph nodes and resection margins during surgery for perihilar cholangiocarcinoma (PHCC). Optical molecular imaging of PHCC associated biomarkers is a promising technique to accommodate this need. The biomarkers Vascular Endothelial Growth Factor (VEGF-A), Epidermal Growth Factor Receptor (EGFR) and c-MET are overexpressed in PHCC versus normal tissue and are proven to be valid targets for molecular imaging. Currently, tracers that target these biomarkers are available for use in clinical studies. In previous studies with other tumour types, we tested the tracer bevacizumab-IRDye 800CW for the biomarker VEGF-A with very promising results, therefore we will start with this tracer. We hypothesize that the tracer bevacizumab-IRDye 800CW accumulates in PHCC tissue, enabling visualization using a NIR intraoperative camera system and NIR endoscopy. In this pilot study, we will determine if it is possible to detect PHCC intraoperatively and by NIR endoscopy using bevacizumab 800CW, and which tracer dose gives the best target-to-background ratio. The most optimal tracer dose will be selected for a future phase II trial.

Study objective

Primairy
To assess whether bevacizumab-800CW allows for intraoperative fluorescence imaging of perihilar cholangiocarcinoma and what dose provides the best visualization of tumor tissue by determining the tumor-to-background (TBR) ratio ex vivo

Secondary
Part 1
1.Determine if accumulation of the fluorescent tracer bevacizumab 800CW can be detected
for identification of PHCC during surgery.
2.Determine if accumulation of the fluorescent tracer bevacizumab 800CW can be detected for identification of PHCC during ex vivo endoscopy.

Part 2
Define if the optimal dose of bevacizumab-800CW provides an adequate TBR ratio for use in a future phase II trial. When TBR is found to be too low for bevacizumab-800CW in all three dose groups the study will stop. A new pilot study in patients with hilar cholangiocarcinoma will then be performed with the promising fluorescent tracers cetuximab-800CW or c-met.

Study design

This is an interventional exploratory clinical trial. We will study the fluorescence signal in PHCC after administration of bevacizumab-IRDye 800CW in patients with clinical suspicion of PHCC who are scheduled to undergo surgical intervention.
The primary objective is to assess whether bevacizumab-800CW allows for intraoperative fluorescence imaging of perihilar cholangiocarcinoma and what dose provides the best visualization of tumor tissue. The secondary objectives are to determine if accumulation of the fluorescent tracer bevacizumab 800CW can be detected for identification of PHCC during surgery and NIR endoscopy.
For this purpose, the study will comprise of two parts. In part 1 three small cohorts of a maximum of 3 patients per group will doses of the tracer bevacizumab-IRDye 800CW: 10mg and 25mg subsequently. Depending on the results we will deescalate or escalate to 4.5mg and 50mg respectively. After completion of each cohort efficacy data will be reviewed by determining the fluorescent signal and by calculating the TBR. The dose group with the highest TBR will be expanded to 6 patients. If two dose groups perform equally well, both groups will be expanded to 6 patients. For part 2, we will define if the optimal dose of bevacizumab-800CW provides an adequate TBR ratio for use in a future phase II trial. If the TBR is too low in all three dose groups, the groups will not be expanded and the pilot study will stop. At this point we will rerun the pilot study with the promising tracers cetuximab-800CW or c-Met.

Intervention

In part one a maximum of 15 patients will receive a single bolus injection of bevacizumab-800CW three days before surgery. During surgery, several imaging moments are defined in which the near infrared intraoperative camera system will detect the fluorescent signal. When resection is completed it will be determined if it is also possible to detect fluorescent signal from tumour tissue by ex vivo NIR endoscopy of the bile ducts.

Study burden and risks

Time investment for study participants
PHCC patients who are scheduled for surgery with curative intent at the UMCG are asked to participate in this trial. Once written informed consent is obtained the patient has one study specific visit for administration of the tracer. In addition to the surgical procedure the study related procedures are expected to take up to 15 minutes extra as compared to regular practice.

Risk for study participants
Risks to study participants are mainly related to the, already present, risks of the surgical procedure and to the administration of the tracer. A data safety monitoring board (DSMB) will not be installed as in more than 110 patients receiving bevacizumab-800CW, no (serious) adverse events were observed. For patients who are on combination therapy with Bevacizumab for the treatment

of cancer, it is commonly accepted that the patient can safely undergo surgery 6 weeks after termination of the Bevacizumab therapy: i.e. at this time the anti-angiogenetic effects have diminished sufficiently to assure there is no increased risk of bleeding or post-operative complications. The through plasma levels after 6 weeks wash out of the drug equal the peak plasma levels after a 160mg IV dose (communication and calculations by the Hospital Pharmacy and the department of Medical Oncology at the UMCG). Furthermore, Starlinger et al investigated that even after a cessation time of 6 weeks bevacizumab is fully active and blocks circulating and local VEGF at the time of liver resection, but no increase in perioperative morbidity is recorded1. Since bevacizumab-800CW will be used in a dose far below 160mg it will therefore cause no additional complication risk, as also evaluated in more than 110 patients after receiving bevacizumab-800CW.

Benefits for study participants
The addition of the near infrared fluorescent imaging agent and camera system during PHCC surgery does not have direct benefits for the participating patients. Interference with standard clinical care is not expected since the surgeons are to follow their normal standard of care during tumour resection surgery. If fluorescent signals are detected during surgery in parts that are not part of the surgical specimen, a maximum of 3 biopsies per fluorescent area may be taken to confirm ex vivo analyses if the fluorescent signals represent cancer tissue.

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

- Age older or equal to 18 year
- Patients with suspected perihilar cholangiocarcinoma who are scheduled to undergo surgical intervention with curative intent
- WHO performance score 0-2

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient's ability to give informed consent.
- Other invasive malignancy
- Pregnant or lactating women.
- History of infusion reactions to bevacizumab
- Inadequately controlled hypertension with or without current antihypertensive medications
- Within 6 months prior to inclusion: myocardial infarction, TIA, CVA, pulmonary embolism, uncontrolled chronic hepatic failure, unstable angina pectoris

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-05-2018
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	intraoperative MFRI camera
Registration:	No

Ethics review

Approved WMO Date:	30-04-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-07-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2018-000794-67-NL
ClinicalTrials.gov	NCTnognietbekend
CCMO	NL65378.042.18