Visualization of a VEGF-targeted Optical Fluorescent Imaging Tracer in rectal cancer during flexible Near-Infrared fluorescence endoscopy;A single center feasibility study

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON41418

Source
ToetsingOnline

Brief title
VEGF-targeted fluorescence endoscopy in rectal cancer

Condition

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

Synonym
rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF

Intervention

Keyword: Endoscopy, Fluorescence, Rectal cancer, VEGF

Outcome measures

Primary outcome

The primary objective of this study is to determine the sensitivity of the marker bevacizumab-IRDye800CW using innovative NIR fluorescence endoscopy (visualizing with wide-field endoscopy, measuring with MDSFR/SFF spectroscopy and optionally visualizing with optoacoustic endoscopy), in identifying target expression and heterogeneity prior to the start and after neoadjuvant treatment.

Research aims to assess primary objectives

Evaluation of wide-field, spectroscopy and opto-acoustic images

- Determine positive and negative fluorescent areas of wide-field fluorescence images
- Quantify fluorescence signal of the tumour, tumour margins and surrounding tissue using MDSFR/SFF spectroscopy
- Determine and (semi)quantify fluorescence intensities in deeper (malignant) tissue using opto-acoustic endoscopy

Evaluation of biopsy and surgical specimen

- Identify VEGF expression and heterogeneity

- Assess the (sub-)cellular location of bevacizumab-IRDye800CW and determine fluorescence intensity in biopsy specimen using fluorescence microscopy

- Correlate determined fluorescence (in vivo and ex vivo) to histology, VEGF expression and VEGF heterogeneity.

Evaluation of safety aspects

- To obtain information on safety aspects of the tracer, side effects, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR).

Secondary outcome

The secondary objectives of this study are:

- Study if fluorescence endoscopy can evaluate treatment response after neoadjuvant treatment, just prior to surgery.

- Study if there is a correlation between the outcome of fluorescence endoscopy and other biological and molecular parameters.

- Study if there is a correlation between the outcome of fluorescence endoscopy and circulating tumour DNA.

Research aims to assess secondary objectives

Next to the research aims used to assess the primary objective, the following are used:

- Assess correlation between outcome of fluorescence endoscopy and pathologic response.

- Characterize circulating tumour DNA over time.

- IHC, DNA, RNA and protein analyses on circulating tumour DNA and biopsy and

surgical specimen.

Study description

Background summary

To improve rectal cancer management, there is a need for better visualization of drug targets in rectal cancer to identify patients who might benefit from specific targeted treatments. Molecular imaging of rectal cancer associated targets is a promising technique to accommodate this need. Vascular Endothelial Growth Factor (VEGF), which is differentially expressed in normal versus malignant colon tissue, has proven to be a valid target for molecular imaging. Fluorescent labeling of bevacizumab (a VEGF targeting humanized monoclonal antibody currently used in anti-cancer therapy) has potential advantages in view of safety, infrastructure, costs, stability and imaging resolution. Therefore, the fluorescent tracer bevacizumab-IRDye800CW has been developed at the University Medical Center Groningen (UMCG) and was recently approved to be administered to patients in a tracer dose (NL37479.042.11). To detect this tracer in vivo in patients with colorectal cancer, a newly developed flexible near-infrared (NIR) fluorescence endoscope, MDSFR/SFF spectrofiber and optoacoustic endoscope have been developed which can be used in clinical studies. Optical fluorescence imaging may support response evaluation following chemoradiotherapy and give insight which patient might benefit from anti-VEGF targeted therapy in future studies. In addition, information collected in this study regarding tracer distribution can be used for future studies in which flexible NIR fluorescence endoscopy will be validated for detection of premalignant lesions in the colon and oesophagus.

Study objective

The primary objective of this study is to determine the sensitivity of the marker bevacizumab-IRDye800CW using innovative NIR fluorescence endoscopy (visualizing with wide-field endoscopy, measuring with MDSFR/SFF spectroscopy and optionally visualizing with optoacoustic endoscopy), in identifying target expression and heterogeneity prior to the start and after neoadjuvant treatment.

The secondary objectives of this study are:
- Study if fluorescence endoscopy can evaluate treatment response after neoadjuvant treatment, just prior to surgery.

- Study if there is a correlation between the outcome of fluorescence endoscopy and other biological and molecular parameters.
- Study if there is a correlation between the outcome of fluorescence endoscopy and circulating tumour DNA.

Study design

The current study is a non-randomized, non-blinded, prospective, single center feasibility study to determine whether molecular imaging using NIR fluorescence endoscopy and bevacizumab-IRDye800CW can provide insight into the heterogeneity of the target VEGF in patients with locally advance rectum carcinoma, to identify patients who might benefit from additional targeted anti-VEGF treatment.

Patients with locally advanced rectum carcinoma are allowed to be included in the RAPIDO study (NL36315.042.11). Subjects will undergo two times epi-illumination endoscopy (in other words flexible NIR fluorescence endoscopy). The first endoscopy will be performed at baseline; before the start of chemoradiotherapy. The second endoscopy will be performed within 2 weeks before surgery. The new VEGF-targeting fluorescent tracer (bevacizumab-IRDye800CW) will be administered intravenously two days before the flexible NIR fluorescence endoscopy procedure. During the flexible NIR fluorescence endoscopy procedure we will determine whole tumor distribution of bevacizumab-IRDye800CW to gain insight into tumor heterogeneity. Subsequently, the NIR fluorescent signal in various areas of the lesion will be quantified. Tumors will be imaged using different angles to get optimal excitation of the tissue. We will measure the fluorescence using MDSFR/SFF spectroscopy. We will take targeted biopsies from areas with high and low uptake of the tracer during epi-illumination endoscopy for ex vivo analyses (at least 4 reproducible small biopsies per area to decrease sampling error; 2 for paraffin embedding and 2 for frozen collection). During the first flexible NIR fluorescence endoscopy procedure a standard clinical tattoo will be applied distally of the lesion (6 o*clock position) to enable identical visualization during the second procedure. In addition, areas will be digitally video recorded to enable biopsies of the same area between procedures. Biopsies will be extensively analyzed (described below). Optionally, we will ask patients if they would like to undergo optoacoustic endoscopy. This is a form of endoscopic ultrasound which is able to detect bevacizumab-IRDye800CW up to 2 cm in depth. The procedure is comparable with NIR fluorescence endoscopy. If patients agree, after removal of the NIR fluorescence endoscope the optoacoustic endoscope will be introduced in the rectum of the patient for detection of bevacizumab-IRDye800CW in deeper areas of the tumor.

Intervention

Patients included in this study will be administered Bevacizumab-IRDye800CW

intraveneously in tracer dose (4.5 mg in 5 ml) and observed for one hour. Two days after tracer administration patients undergo flexible near-infrared fluorescence endoscopy with MDSFR/SFF spectroscopy including biopsies and optionally optoacoustic endoscopy. Tracer injection and endoscopy procedure will be performed twice.

Study burden and risks

Burden and risks:
In this study, safety data related to (the administration of) Bevacizumab-IRDye800CW will be collected and evaluated. Based on clinical experience in the first five breast cancer patients (NL37479.042.11), toxicity studies and the fact that we will administrate two times a low, non-therapeutic (single dose 4.5 mg bevacizumab-IRDye800CW vs 5 mg/kg bevacizumab in therapeutics), no adverse events are expected following administration of bevacizumab-IRDye800CW. A possible side-effect following administration is a raised blood pressure. Tracer administration will take one hour, since the patients are observed for one hour post administration.

In the current protocol, patients will undergo fluorescence endoscopy; a comparable procedure to standard clinical sigmoid endoscopy with bowel cleaning by a phosphate enema. The risks of the investigational procedure are comparable to the minimal risks of a standard clinical sigmoid endoscopy. Small superficial biopsies will be taken. These biopsies have minimal risk of bleeding, which mostly coagulate spontaneously. If not, which is very uncommon, the gastroenterologist has several tools to attack this small bleeding. The procedure will take 20 minutes and is performed by experienced gastroenterologists. Optionally, patients will undergo optoacoustic endoscopy following fluorescence endosocpy to detect bevacizumab-IRDye800CW in deeper areas of the tumor. This procedure will take 10 minutes.

The time investment of the subjects is considered reasonable. The procedures at the screening visit, the tracer administration visit and the endoscopy procedure will take 1 to 2 hours, depending on the visit.

Benefit:
Patients are treated following standard clinical care or according to the RAPIDO study protocol. Additional NIR fluorescence endoscopy will not have any benefits for the participating patients.

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

Patients with locally advanced rectal cancer.
- Rectal cancer, in multi disciplinary colorectal oncology meeting agreed on long course neoadjuvant chemoradiotherapy or neoadjuvant treatment according to RAPIDO trial.
- Age * 18 years.
- Written informed consent.

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent.
- Concurrent uncontrolled medical conditions.
- Pregnancy or breast feeding.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-10-2013
Enrollment:	30
Type:	Actual

Medical products/devices used

Generic name:	Clinical therapeutic endoscope;fiber bundle to perform near infrared fluorescence endoscopy and a MD
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	04-03-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	06-06-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	18-12-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	12-01-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-05-2016
Application type:	Amendment
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	EUCTR2013-000333-12-NL
CCMO	NL43407.042.13