A pilot intervention study for the use of VEGF-targeted Fluorescence Near-Infrared (NIR) Endoscopy in (pre)malignant Esophageal Lesions

Published: 13-02-2014
Last updated: 20-04-2024

The primary objective of this pilot intervention study is to determine the sensitivity of the fluorescent tracer bevacizumab-IRDye800CW using a flexible NIR fluorescence endoscope in identifying (pre)malignant esophageal lesions during endoscopy....

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

Summary

ID

NL-OMON41226

Source
ToetsingOnline

Brief title
VICE

Condition

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

Synonym
Esophageal adenocarcinoma; esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Esophageal cancer, Fluorescence, Near-Infrared (NIR) endoscopy, VEGF

Outcome measures

Primary outcome

- Macroscopic fluorescent signal levels and tracer distribution observed by flexible NIR fluorescence imaging; (semi)quantitative.

- Microscopic distribution and objecifying of the fluorescent signal intensity of bevacizumab-IRDye800CW in vivo using the CLE cellvizio probe-based imaging system.

- Microscopic distribution and (semi)quantitative fluorescent signal intensity of bevacizumab-IRDye800CW in the EMR specimen and biopsies correlated to VEGF distribution and level of expression

Secondary outcome

- Distinguish and objectify in vivo the NIR fluorescent signal of Bevacizumab-800CW by means of the CLE cellvizio probe-based imaging system.

- The correlation between fluorescence intensity and the grade of VEGF expression on immunohistochemistry, in (pre)malignant lesions of the esophagus.

- Adverse events (AE), serious adverse events (SAE), and suspected unexpected serious adverse reactions (SUSARs).

Study description

Background summary

Esophageal cancer is with approximately 500.000 new esophageal cancer cases annually, the eight most commonly diagnosed type of cancer globally. Esophageal cancer is associated with a high mortality, estimated at approximately 400.000 deaths annually, and therefore the fifth leading cause of cancer associated deaths worldwide. Next to this, the incidence of esophageal adenocarcinoma (EAC) has shown to rise dramatically over the past few decades.

To improve detection of esophageal (pre)malignant lesions during surveillance endoscopy of patients at risk of developing malignancies, for example in Barrett*s Esophagus (BE), there is a need for better endoscopic visualization and the ability for targeted biopsies. Optical molecular imaging of neoplasia associated biomarkers could form a promising technique to accommodate this need. It is known that the biomarker Vascular Endothelial Growth Factor (VEGF) is overexpressed in dysplastic and neoplastic areas in BE segments versus normal tissue and has proven to be a valid target for molecular imaging. The University Medical Center Groningen (UMCG) developed a fluorescent tracer by labeling the VEGF-targeting humanized monoclonal antibody bevacizumab, currently used in anti-cancer therapy, with the fluorescent dye IRDye800CW. We hypothesize that when bevacizumab-IRDye800CW is administered, it accumulates in VEGF expressing high grade dysplasia (HGD) and esophageal adenocarcinoma (EAC), enabling early cancer visualization using a newly developed flexible Near-Infrared (NIR) fluorescence endoscopic platform. We want to test this hypothesis in this pilot intervention study.

Study objective

The primary objective of this pilot intervention study is to determine the sensitivity of the fluorescent tracer bevacizumab-IRDye800CW using a flexible NIR fluorescence endoscope in identifying (pre)malignant esophageal lesions during endoscopy.

The in vivo fluorescent signal of early carcinoma (HGD and superficial EAC), measured with the NIR fluorescence endoscopic platform, will be analyzed. The accumulation of bevacizumab-IRDye800CW and the VEGF expression levels will be analyzed ex vivo in the resected mucosal specimen. To assess the primary objective, these results will be compared.

This study should support future studies using bevacizumab-IRDye800CW and flexible NIR fluorescence endoscopy for the purpose of improving surveillance strategies in high risk populations of developing gastrointestinal dysplasia and adenocarcinoma, such as patients with known BE.

Secundaire objectives:
- To collect safety data of Bevacizumab-IRDye800CW.
- To investigate the correlation between fluorescence intensity and the grade of VEGF expression in (pre)malignant lesions of the esophagus.
- To evaluate if there is a correlation between in vivo fluorescence intensity and grade of ex vivo VEGF expression .
- To evaluate the degree of in vivo fluorescence intensity and ex vivo grade of VEGF expression for the different stages of esophageal dysplasia-carcinoma sequence.

Study design

The current study is a non-randomized, non-blinded, prospective, single center pilot intervention study to determine whether optical molecular imaging using bevacizumab-IRDye800CW and the newly developed NIR fluorescence endoscope can identify (pre)malignant esophageal lesions.

A selected group of patients, with prior diagnosed HGD or superficial EAC and therefore candidate for endoscopic therapy using a endoscopic mucosal resection (EMR) technique, will receive topical administration of the VEGF-targeting fluorescent tracer bevacizumab-IRDye800CW.

Patients will undergo the endoscopic procedures clustered in one endoscopy-session: topical tracer application with use of spray-catheter (under white-light inspection) followed by NIR fluorescence endoscopy (fiber-bundle and CLE probe; both inserted subsequently through working channel of white-light endoscope). Afterwards the standard therapeutic endoscopic mucosal resection (EMR) will be performed. Next to this, biopsies of normal squamous epithelium and, if present, the BE segment will be taken for study purposes only. These specimens will be analysed ex vivo, using immunohistochemistry and RNA and DNA analysis.

Intervention

Patients included in this study will undergo an endoscopic procedure including the standard endosocpic treatment (EMR) as well as VEGF-targeted fluorescence imaging. All patients will receive the same consecutive endoscopic procedures performed by the same gastroenterologist.

The procedure will start by topically spraying the fluorscent tracer (bevacizumab-800CW) onto the esophageal mucosa. After several minutes of incubation, excessive product will be rinsed. NIR-imaging will take place, by using a NIR fiber-bundle and CLE-probe which can be subsequently inserted through the working channel of the WL-endoscope. Subsequently, during normal

WLE imaging, the EMR procedure will be carried out. Next tot this, a maximum of sixteen biopsies will be taken.

According to standard EMR-protocol, patients will be hospitalized the evening prior to the procedure. As described in the standard EMR-protocol, fasting will start at midnight prior to the procedure . EMR specimens and biopsies will be analyzed ex vivo, using specimen procedures consisting of formalin fixed paraffin embedded and frozen sections.

Study burden and risks

Time investment:
The study consists of one visit: consecutive fluorescence and white-light endoscopy (EMR). The time investment of the participating subjects is considered low; the endoscopy procedure will be prolonged slightly (aprox. 30 min) compared to a standard EMR procedure. According to standard EMR-protocol, patients will be hospitalized the evening subsequent to the procedure. Due to this, and the fact that the patients are under propofol sedation they will not notice the slight prolongation of the procedure. Depending on the procedure and occurrence of possible complication, patients sometimes have to stay hospitalized a subsequent night. As according to standard protocol, fasting will start at midnight prior to the procedure.

Risks:
The additional risks of participating in this study are mainly related to the administration of Bevacizumab-IRDye800CW. Animal toxicological studies on bevacizumab-IRDye800CW and preclinical tracer evaluation data showed no adverse effects. The tracer has been safely intravenously administered to patients in several trials ((NL37479.042.11; NL43407.042.13; NL45148.042.13). Adverse Events may be expected after administration, based on our experience with administrating a higher dose of unlabeled bevacizumab for therapeutic purposes. Hypersensitivity reactions, wound-healing problems and hypertension can occur after therapeutic dosages of intravenous bevacizumab. However, the expected adverse events are temporal without clinical consequences and the risk is considered minimal due to the low tracer dose used and topical administration.

The proposed endoscopy procedure is in intent equal to the therapeutic endoscopic procedure, as the NIR-fiber and CLE-probe will be inserted through the working channel of the WL-endoscope. Next to this, during the WLE procedure max. 16 biopsies will be taken for study purposes only. This has in general a minimal risk of bleeding. Though, if these complications occur, which is very uncommon, the gastroenterologist has several tools to handle these problems adequately.

Benefit:
The investigational endoscopy procedure does not have direct benefits for the participating patients. However, the investigational procedure won*t interfere

with standard clinical care, since the fluorescence imaging will be performed in serial with the white-light therapeutic endoscopy. Given the limited extra time investment, the honorable minimal risks and the medical need for improved diagnostic capabilities it seems therefore justified to ask to participate in this study. Moreover, it is expected that this research will provide useful information when considering future patient care and diagnostic endoscopy. Hopefully, the results of this feasibility study will contribute to the improvement of esophageal cancer detection and surveillance.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Identified high grade dysplasia (HGD) or intramucosal adenocarcinoma (EAC; T1) and therefore candidate for endoscopic therapy using EMR.

- Mentally competent person, age 18 years or older
- Written informed consent.
- Adequate potential for follow-up.

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent.
- Submucosal and invasive EAC ; EAC with TNM-classification other than T1
- Concurrent uncontrolled medical conditions or medical conditions which disqualify for an EMR procedure.
- Previously preformed therapeutic endoscopic procedures.
- 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):	29-04-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	Clinical therapeutic endoscope;NIR fluorescent fiberbundle;CLE-probe
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	13-02-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-04-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-03-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2015
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	EUCTR2013-003003-19-NL
ClinicalTrials.gov	NCT02129933
CCMO	NL45554.042.14

Study results