A phase 2 intervention study: Detection of early esophageal neopastic lesions by quantified fluorescence molecular endoscopy using oral and topical administration of bevacizumab-800CW and cetuximab-800CW

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Primary objectives:The primary objectives are to evaluate the feasibility of oral administration of bevacizumab-800CW and cetuximab-800CW for detection of neoplasia in BE patients compared to HD-WLE to shorten the qFME procedure and test whether…

Ethical review	Approved WMO
Status	Pending
Health condition type	Benign neoplasms gastrointestinal
Study type	Interventional

Summary

ID

NL-OMON53297

Source
ToetsingOnline

Brief title
Oral fluorescent tracer administration to detect esophageal adenocarcinoma

Condition

- Benign neoplasms gastrointestinal
- Gastrointestinal neoplasms malignant and unspecified

Synonym

Barrett's esophagus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Barretts esophagus, Esophageal adenocarcinoma, Fluorescence molecular endoscopy, Spectroscopy

Outcome measures

Primary outcome

Primary objectives:

The primary objectives are to evaluate the feasibility of oral administration

of bevacizumab-800CW and cetuximab-800CW for detection of neoplasia in BE

patients compared to HD-WLE to shorten the qFME procedure and test whether

combined tracer administration increases lesion detection.

Secondary outcome

Secondary objectives:

1. To collect safety data on oral administration of (combined)

bevacizumab-800CW and cetuximab-800CW by spraying.

2. To (semi)quantify and evaluate the in vivo NIR fluorescent signal of

bevacizumab-800CW and cetuximab-800CW combined by using the spectroscopy probe

and compare this to the ex vivo VEGFA/EGFR levels in the resected mucosal

lesions and/or biopsies taken.

3. Eventually further specify and objectify the improvement of qFME by

standardization and tracer administration, by dose optimization, leading to

reduction of unnecessary biopsies.

Study description

Background summary

Patients with Barrett*s esophagus (BE) have an increased risk of developing esophageal adenocarcinoma (EAC). Esophageal adenocarcinoma (EAC) causes six percent of cancer related deaths worldwide, with studies predicting a rise in the incidence of EAC. Early diagnosis is challenged by asymptomatic disease progression. Consequently, late-stage detection translates to a five-year survival rate of 15 - 20%. Current endoscopic surveillance with random biopsies according to the Seattle protocol is costly and time-consuming with a potential high miss rate. This stresses the great need for better endoscopic visualization and thereby the ability to take targeted biopsies to improve detection of esophageal (pre)malignant lesions during surveillance endoscopy of patients at risk of developing these esophageal malignancies. Optical molecular imaging of neoplasia associated biomarkers seems a promising technique to accommodate this need. It is known that several biomarkers are overexpressed in dysplastic and neoplastic tissue and these biomarkers can be a valid target for quantified fluorescence molecular endoscopy (qFME).

One of these biomarkers is vascular endothelial growth factor A (VEGFA). The phase I study, named VICE, completed within the UMCG, showed that synchronal use of VEGFA-guided quantified fluorescence molecular endoscopy and high-definition white light endoscopy (HD-WLE) with narrow-band imaging (NBI) could improve early lesion detection by 33% using the topically applied tracer approach compared to HD-WLE/NBI endoscopy. Within the phase II study, the ESCEND study, we further evaluated topical administration of bevacizumab-800CW and qFME in sixty patients (unpublished data). qFME with bevacizumab-800CW detected 71 lesions compared to 56 lesions detected by HD-WLE/NBI performed by the BE expert endoscopist (+27%) and 33 lesions detected by the non-BE expert endoscopist (+115%). Additionally, two other tracers were investigated in a smaller subset of patients, cetuximab-800CW, targeting epidermal growth factor receptor (EGFR) and the nonspecific near-infrared fluorescent dye indocyanine green (ICG). qFME with cetuximab-800CW detected 17 lesions compared to 12 lesions detected by HD-WLE/NBI performed by the BE expert endoscopist (+42%) and 9 lesions detected by the non-BE expert endoscopist (+89%). The ESCEND study has confirmed the great potential of qFME looking at additional lesion detection initially missed by HD-WLE, especially compared to non-BE expert centers.

However, we hypothesized, that we can potentially identify more additional lesions by simultaneous use of two targeted tracers because of variable

expression of VEGFA and EGFR within EAC. Until now, solely intravenous and topical administration of the tracers has been investigated. However, optimization of tracer administration and shortened incubation is necessary for clinical translation and implementation of this new technique from BE expert centers to regional non-expert centers. BE surveillance procedures normally takes up to 15 minutes at regional hospitals, of which most of the procedural time is needed to take biopsies according to the Seattle protocol. Introducing qFME into these hospitals would elongate the procedure time with at least 10 - 15 minutes. This would increase healthcare costs and put increased pressure on BE healthcare. Ideally, the gastroenterologist can immediately start with the qFME procedure without any incubation time while maintaining the best TBR possible. Oral administration by drinking the tracer prior to the procedure would eliminate incubation time and its consequences. Quantified qFME with oral tracer administration and targeted biopsies could potentially replace the time-consuming, high miss rate Seattle protocol, improve lesion detection and decrease global healthcare costs associated with BE.

Therefore, we propose to investigate the following:
1. Can qFME procedural time be diminished by oral administration of the fluorescent tracer(s)?
2. Does combining bevacizumab-800CW and cetuximab-800CW improve lesion detection compared to single tracer administration?

Study objective

Primary objectives:
The primary objectives are to evaluate the feasibility of oral administration of bevacizumab-800CW and cetuximab-800CW for detection of neoplasia in BE patients compared to HD-WLE to shorten the qFME procedure and test whether combined tracer administration increases lesion detection.

Secondary objectives:
1. To collect safety data on oral administration of (combined) bevacizumab-800CW and cetuximab-800CW by spraying.
2. To (semi)quantify and evaluate the in vivo NIR fluorescent signal of bevacizumab-800CW and cetuximab-800CW combined by using the spectroscopy probe and compare this to the ex vivo VEGFA/EGFR levels in the resected mucosal lesions and/or biopsies taken.
3. Eventually further specify and objectify the improvement of qFME by standardization and tracer administration, by dose optimization, leading to reduction of unnecessary biopsies.

Study design

The study design consists of three study arms. An overview of the study design is shown in figure 1. Arm 3 will only be performed if oral administration is

not feasible. We want to include non-dysplastic BE as control group to confirm that our fluorescent tracers do not bind to Barrett tissue without a lesion to show their specificity.
1. Oral bevacizumab-800CW in dysplastic BE
2. Oral cetuximab-800CW and combined oral bevacizumab-800CW/cetuximab-800CW in dysplastic BE or oral bevacizumab-800CW in non-dysplastic BE
3. Topical bevacizumab-800CW and combined topical bevacizumab-800CW/cetuximab-800CW in dysplastic and non-dysplastic BE

After signing of the informed consent by both the patient and the study investigator, the patient will undergo the combined procedure (qFME and HD-WLE with biopsies or EMR/ESD). In case of EMR/ESD, the procedure will be performed under propofol sedation and therefore the patient*s vital parameters will be monitored closely by an employee of anesthesiology department (standard clinical care).

In arm 1 and 2, patients will receive oral tracer administration and are asked to drink Infacol to clean the esophagus. This is standard care before endoscopy procedures. The tracer bevacizumab-800CW and/or cetuximab-800CW will by orally administered by drinking two cups of 15 ml in an upright position around ten minutes before the study procedure. Endoscopic procedures will be performed by a specialized BE endoscopist. The procedure will start with HD-WLE inspection. Subsequently, NIR-imaging will take place, by using a fiber-bundle for fluorescence molecular endoscopy and spectroscopy probe, which can both be inserted subsequently through the working channel of the HD-WLE. The HD-WLE suspected (pre)malignant lesion, normal esophageal epithelium, gastric mucosa and, when present, non-dysplastic BE segment will be evaluated according to their fluorescent intensity. Biopsies will be taken according to the Seattle protocol. All endoscopically visible lesions will be biopsied (maximum of 6), followed by four-quadrant biopsies with 2 cm interval from the lower esophageal sphincter to the squamocolumnar junction (10,11). All biopsies will be formalin fixed paraffin embedded (FFPE).

We will perform an EMR/ESD during the therapeutic procedure instead of taking biopsies from additional fluorescent lesions detected with qFME that were initially missed by HD-WLE. qFME shows a high positive predictive value of 96%. The positive predictive value might even be higher because of sampling error where qFME can detect fluorescence while biopsies do not reach the depth of the dysplasia. We think that this is sufficient evidence to support that a therapeutic EMR/ESD of invisible fluorescent lesions being beneficial for the patient. An EMR/ESD is associated with < 1 % risk of perforation and bleeding. Fluorescence endoscopy procedures will be digitally documented. The complete procedure will be recorded.

The oral administration will be suspended if no accumulation of bevacizumab-800CW in (pre)malignant lesions can be demonstrated in the dose finding stage. We will then continue directly to arm 3 of the study design

where we topically administer bevacizumab-800CW and compare this to combined topical tracer administration with bevacizumab-800CW and cetuximab-800CW.

In arm 3 of the study design, that will only be performed when oral tracer administration is not feasible, patients will receive topical tracer administration and the esophagus will be cleaned with acetyl cysteine 0.1% at the beginning of the procedure. After standard HD-WLE, patients will be topically administered by spraying the tracer(s) with subsequent standard 5 minutes incubation time. Followed by rinsing the esophagus with water to wash away unbound tracer after which qFME can be performed.

Biopsies will be taken according to the Seattle protocol. The biopsies will be processed in the same manner as standard clinical biopsies. If necessary, the procedure is followed by routine EMR/ESD performed by the same physician performing the standard procedure. EMR/ESD specimens and biopsies will be analyzed ex vivo and as a fresh specimen analyzed FFPE, according to the standard procedure. Elderly patients with relevant comorbidity will be hospitalized the evening prior to the procedure when there is a scheduled EMR/ESD, according to standard EMR/ESD-protocol. In some cases, treated patients will stay hospitalized a subsequent night.

Moreover, the study will be suspended immediately if any severe adverse event (SAE) related to the administration of the tracers occurs in any of the patients. The design of this study warrants maximal data collection, while risks and burden for patients are minimized.

Intervention

Patients will receive oral administration of the tracer bevacizumab-800CW and/or cetuximab-800CW prior to the endoscopy procedure During the procedure standard HD-WLE together with fluorescence endoscopy and MDSFR/SFF spectroscopy will be performed. Furthermore we will collect biopsies according to standard Seattle protocol. We will perform an EMR/ESD during the therapeutic procedure instead of taking biopsies from additional fluorescent lesions detected with qFME that were initially missed by HD-WLE because fluorescence endoscopy shows a high positive predictive value of 96%. Patients will be sedated during the endoscopic procedure following standard clinical care procedures.

Study burden and risks

The administration risks of bevacizumab-800CW and cetuximab-800CW are reported in the investigational medicinal product dossier (IMPD) (bevacizumab-800CW: version 6.0, June 2020, section 2.4, cetuximab-800CW: version 2.0, June 2020, section 2.4). No adverse events were reported from previous administrations with bevacizumab-800CW with more than 120 patients included. Bevacizumab-800CW will be orally administered in 4.5 mg and 9 mg, which is a 50 - 100 times lower

dose than therapeutic bevacizumab. Therefore, no (serious) adverse events are expected. Topical administration of cetuximab-800CW did not show any adverse events in the ESCEND study. Bevacizumab-800CW and cetuximab-800CW are both human monoclonal antibodies and are not expected to interact with anything else than their own target. It is not expected that the intact antibody is taken up after esophageal passage as it is expected to be dissolved by gastric acids.

Oral administration can increase the risk of choking after swallowing the tracer, especially in patients with reflux disease associated with a higher prevalence of swallowing impairment. However, administration of the tracer will be performed in a controlled hospital environment where the patient is prepared for the endoscopy procedure according to standard care. Patients normally drink Invacol from an open cup before a procedure. The staff is well trained and can react to adverse events when adverse events related to swallowing occur. We will ask the patient at the start whether there were problems with drinking the tracer from an open cup.

The endoscopic procedure will be prolonged with 15 minutes to enable fluorescence imaging (qFME and MDSFR/SFF). The fiber of qFME or MDSFR/SFF can be inserted through the working channel of HD-WLE endoscope and therefore the risks of fluorescence imaging are comparable to standard HD-WLE endoscopy and assumed negligible. The biopsy procedure may cause some bleeding which resolves spontaneously and does only need intervention in very rare cases (1 per 5000 endoscopies per year).

We have confirmed the potential of qFME in the phase II ESCEND study. Based on these results, we want to perform an EMR/ESD during the therapeutic procedure instead of taking biopsies from additional fluorescent lesions detected with qFME. qFME shows a high positive predictive value of 96% when confirming fluorescent lesions as dysplasia by pathology. Three lesions were marked positive by qFME while biopsies could not confirm dysplasia. The positive predictive value might even be higher because of sampling error where qFME can detect fluorescence while biopsies do not reach the depth of the dysplasia. We think that this is sufficient evidence to support a therapeutic EMR/ESD of invisible fluorescent lesions being beneficial for the patient. An EMR/ESD is associated with < 1 % risk of perforation and bleeding.

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

- BE patients without dysplasia and with suspected/diagnosed LGD, HGD or superficial EAC and planned diagnostic and/or therapeutic endoscopy
- Written informed consent is obtained

Exclusion criteria

- Patients under the age of eighteen.
- Submucosal and invasive EAC, also defined as EAC with TNM-classification other than T1.
- Previous radiation therapy for esophageal cancer
- Known immunoglobulin allergy
- Previous chemotherapy, immunotherapy or related surgery
- Prior bevacizumab or cetuximab treatment
- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent
- Pregnancy or breast feeding.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-05-2023
Enrollment:	25
Type:	Anticipated

Medical products/devices used

Generic name:	A clinical therapeutic endoscope;a fiber bundle to perform fluorescence endoscopy and a MDSFR/SFF sp
Registration:	No
Product type:	Medicine
Brand name:	Bevacizumab-800CW
Generic name:	Avastin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Cetuximab-800CW
Generic name:	Erbitux
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	22-05-2023
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	EUCTR2023-503801-12-NL
ClinicalTrials.gov	NCT05745857
CCMO	NL83861.042.23