A pilot study to assess the safety and feasibility of fluorescent sentinel lymph node identification in colon carcinoma using intravenous bevacizumab-800CW

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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-OMON53524

Source
ToetsingOnline

Brief title
IBIZA-2(pilot)

Condition

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

Synonym
colon carcinoma, intestinal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Meander Medisch Centrum
Source(s) of monetary or material Support: Meander Medisch Centrum

Intervention

Keyword: Bevacizumab-800CW, Colon carcinoma, Fluorescence, Sentinel lymph node

Outcome measures

Primary outcome

The primary outcome parameters are identification rate of SLN(s) or lymph node metastases with bevacizumab-800CW, defined as the number of patients in which a SLN or lymph node metastasis was detected due to fluorescence during surgery and/or pathology assessment divided by the total number of procedures.

Furthermore the rate of adverse events related towards bevacizumab-800CW will be measured. This is defined as the number of adverse events related towards bevacizumab-800CW/total number of procedures.

Secondary outcome

Secondary outcome parameters include: amount of fluorescence in lymph node metastases compared to lymph node without metastases, false-negative SLNs, true-negative SLNs, sensitivity, upstaged patients, aberrant lymph node status, accuracy, negative predictive value and number of SLNs identified.

Study description

Background summary

The current gold standard for the treatment of colon carcinoma consists of the surgical en-bloc resection of the colonic segment including the adjacent mesocolon containing the draining lymph nodes. Analysis of these lymph nodes is

important, since lymph node status is one of the most important prognostic factors determining the use of adjuvant chemotherapy. Although patients with tumour stage I and II do not have lymph node metastases, 15-20% develop recurrent disease. Several studies suggest that ultrastaging techniques such as immunohistochemistry (IHC) or reverse transcriptase polymerase chain reaction (RT-PCR) using multilevel slicing results in upstaging of 14-18% of patients, due to newly found (micro)metastasis. Furthermore, several studies indicate that these micrometastases are correlated with a significantly poorer prognosis, subsequently suggesting that this subgroup of patients might benefit of adjuvant chemotherapy. Therefore, the most recent Dutch guidelines advice the use of adjuvant chemotherapy in this *upstaged* group, although evidence is still lacking.
However, ultrastaging techniques are labour-intensive and costly, and therefore not suitable for analyses of all lymph nodes that have been collected during segmental colectomy. Sentinel lymph node (SLN) identification in colon carcinoma has been proposed to overcome this problem by identifying the first order draining lymph node(s) of the tumour, which have the highest chance of containing metastatic tumour cells. Several studies aimed at SLN identification in colon carcinoma have been published, however, early studies using radio-guided or blue-dye guided SLN identification, showed relatively high rates of false negatives with consequent low sensitivity rates. Since mesocolon is rather fatty tissue, visualization of conventional dyes is difficult. Indocyanine green (ICG), which can be visualized using near infrared (NIR), has been put forward since it is known to penetrate relatively deep into living tissue.
Nevertheless, results of SLN identification using ICG remain unsatisfying with high false-negative rates and low sensitivity. Most likely this is due to the fact that these studies also included large cT3-cT4 tumours and patients with massive lymph node involvement. Which are factors known to interfere with lymph drainage patterns. Furthermore, subserosal injections were frequently used, while it is suggested that submucosal injections might result in better sensitivity of the procedure. In the FLUOR-SLN-ICG pilot study, we successfully conducted SLN identification in patients with ICG.

Recently, more research is conducted in tumour-targeted tracers as they have many advantages compared to ICG. For example, tumour-targeted tracers can be preoperatively administered which aid logistics, binds to tumour and metastases, thus allowing more time for uptake in patients with larger tumours and lymph node metastases. These properties may result in increased accuracy and would be more broadly applicable compared to ICG. Furthermore, tumour-targeted tracers can also be administrated intravenously and potentially identify lymph node metastases without having to perform a colonoscopy. However, administration via colonoscopy of tumour-targeted tracers for the detection of lymph node metastases in colon carcinoma has not been performed yet, and intravenous administration would be a step after administration via colonoscopy.
Therefore this prospective study aims to assess the safety and feasibility of

lymph node identification using bevacizumab-800CW in patients with cT1-3N0-2 tumours, using intravenous administration.

Study objective

The primary outcome parameters are identification rate of SLN(s) or lymph node metastases with bevacizumab-800CW, defined as the number of patients in which a SLN or lymph node metastasis was detected due to fluorescence during surgery and/or pathology assessment divided by the total number of procedures. Furthermore the rate of adverse events related towards bevacizumab-800CW will be measured. This is defined as the number of adverse events related towards bevacizumab-800CW/total number of procedures.
Secondary outcome parameters include: amount of fluorescence in lymph node metastases compared to lymph node without metastases, false-negative SLNs, true-negative SLNs, sensitivity, upstaged patients, aberrant lymph node status, accuracy, negative predictive value and number of SLNs identified.

Study design

This is a single-centre, open-label, non-randomized cohort safety and feasibility study.

Intervention

1. Patients are identified at the outpatient clinic and asked for participation in the study.
2. Patients will be planned for laparoscopic/robot-assisted surgical colectomy according to standard of care (SOC).
3. 2-4 days before surgery, 15mg bevacizumab-800CW is intravenously administered. The patient is observed during one hour after injection of bevacizumab-800CW.
4. During segmental colectomy, a NIR camera is used to visualize the SLN, which will be marked using a stitch. If an aberrant lymph node is visualized, this node will be harvested.
5. Segmental colectomy with procurement of the adhering mesocolon will be performed according SOC.
6. After extraction of the specimen, ex-vivo examination of the specimen using the NIR camera will be performed.
7. Postoperative management will be according SOC.
8. Pathological examination will be done using haematoxylin & eosin (H&E). If no lymph node metastases are found, the lymph nodes will be examined using serial slicing and subsequent IHC.
9. Histological section of formalin-fixed paraffin embedded blocks of tissue will also be examined in the UMC Groningen for the presence of NIR. This process will not interfere with standard working procedures related to clinical care. In case no SLN can be detected with intraoperative fluorescence, we will

be able to detect (ex vivo) fluorescence with specially designed cameras present at the UMCG. These cameras can detect bevacizumab-800CW while more than >16.000x diluted. This allows for *ex-vivo* SLN identification if there is any clinically relevant fluorescence present in the lymph nodes, while no intraoperative fluorescence is detected. Therefore, these results then still can be translated to the clinic when optimised systems become available.

Study burden and risks

The potential benefits or harms of the patients are based on the difference in staging that could potentially be an effect of the ultrastaging techniques. If macrometastases or micrometastases are detected during ultrastaging techniques, patients will be given adjuvant chemotherapy, according to the Dutch Guideline Colorectal Carcinoma. A potential benefit of this study could be that patients receive adjuvant chemotherapy, due to outcomes of ultrastaging techniques, while they would not receive adjuvant chemotherapy if regular staging techniques were used. Furthermore, aberrant lymph nodes will be excised and analysed as the other lymph nodes. Potentially resulting in treatment with adjuvant chemotherapy while, this would not be given if the aberrant node would not be excised.
In this study, safety data related to (the administration of) bevacizumab-800CW, a targeted optical fluorescent tracer, will be collected and evaluated. VEGF-A (Vascular Endothelial Growth Factor-A) is highly upregulated in tumour tissue of colorectal origin (UMCG data set: (n=35), 100%) and can be targeted by using bevacizumab (Avastin®, Roche). Bevacizumab is a recombinant, high affinity, humanized IgG1 monoclonal antibody with specific affinity for VEGF-A.
The infrared dye IRDye800CW (LI-COR Biosciences, Lincoln, NE, USA) is a fluorescent dye applicable for clinical use, produced by REGIS technologies. Conjugation of the fluorescent dye to bevacizumab, purification and formulation will be performed at the department of hospital and clinical pharmacy of the UMC Groningen to create bevacizumab-800CW. The new tracer bevacizumab* IRDye800CW has been evaluated preclinical in tumour bearing nude mice and an extended single microdose toxicity study has been performed by NOTOX, which did not show toxicity (more information can be found in the IMPD).
Several studies using bevacizumab-800CW (see ClinicalTrials.gov NCT02113202 , NCT01972373 , NCT02129933 , NCT01508572 , NCT03913806 , NCT03877601 , NCT04212793 , NCT03620292) or other targeted fluorescent agents (see ClinicalTrials.gov NCT01987375, NCT02415881) have received regulatory approvals to administer the non-FDA approved targeted fluorescent agents to humans.
Five studies using bevacizumab-800CW in a total of 91 patients have been completed. In 82 of the 91 patients a dosage of 4.5-50mg bevacizumab-800CW was administered, the remaining nine patients received topical bevacizumab-800CW . Adverse events were observed in only one study. The study used systemic and topical bevacizumab-800CW for guidance during endoscopic mucosal resection. Four adverse events were observed in 14 patients, all adverse events are known

complications of endoscopic mucosal resection: bleeding (n=2), nausea/headache (n=1) and fever (n=1). Thus, most likely these events were not tracer-related . The time investment of participants is considered reasonable. The visit for the tracer administration visit will take around 2 hours total.

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

- Oral and written informed consent (IC)
- Aged 18 years and older
- Pathologically confirmed and/or suspected cT1-3N0-2M0 colon carcinoma

Exclusion criteria

- Distant metastasis
- Suspicion of cT4 disease based on pre-operative assessment
- Metastatic or T4 disease discovered during intraoperative staging
- Pregnancy, lactation or a planned pregnancy during the course of the study
- Previous colon surgery, excluding appendectomy.
- Contra-indication for laparoscopic/robotic surgery
- Inadequately controlled hypertension with or without current antihypertensive medication.
- Within 6 months prior to inclusion: myocardial infarction, TIA, CVA, pulmonary embolism, unstable angina pectoris, or uncontrolled chronic hepatic failure.
- Regarding bevacizumab: Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies. Or an allergy for its components (Trehalose dehydrate, sodium phosphate, polysorbate 20, water for injections)

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):	27-01-2023
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	12-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	13-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-09-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2021-006796-41-NL
CCMO	NL80117.100.21

Study results

Date completed:	10-10-2023
Actual enrolment:	5