Intraoperative detection of tumor tissue in pancreatic cancer using a VEGF-targeted optical fluorescent imaging tracer

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Part 1 1. Determine if accumulation of the fluorescent tracer bevacizumab-800CW can be detected for identification of pancreatic cancer tissue during surgery.2. Identify two doses of conjugate that provide the best visualization of tumor tissue...

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

Summary

ID

NL-OMON44846

Source
ToetsingOnline

Brief title
Image guided surgery in pancreatic cancer

Condition

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

Synonym
cancer of the pancreas, pancreatic cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: FP7 project BecaCure

Intervention

Keyword: fluorescence, intraoperative, pancreatic cancer, VEGF

Outcome measures

Primary outcome

ntraoperative assessment of positive margins as well as positive lymphnodes and metastases based on fluorescent images. *

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

* Standard histopathological examination to compare the fluorescent signals with the presence of malignancy as well as to compare non-fluorescence lesions with the absence of malignancy.

* 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.)

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

Secondary outcome

net

Study description

Background summary

De prognosis for patients with pancreatic cancer is poor. The combination of pre- and intraoperative limitations in staging results in 50%-75% positive margin rates (tumor < 1mm of the resection margin, R1 resection)) in standard of care for surgery with curative intent (4-6,38). Therefore, they need a technology that intraoperatively detects tumor affected tissue accurately and reliably in PDAC. There is a need for better visualization of resection margins and detection of small tumor deposits during surgery for pancreatic cancer. Optical molecular imaging of pancreatic ductal adenocarcinoma associated biomarkers is a promising technique to accommodate this need. The biomarker Vascular Endothelial Growth Factor (VEGF-A) is overexpressed in pancreatic cancer tissue versus normal tissue and has proven to be a valid target for molecular imaging. We hypothesize that bevacizumab-800CW accumulates in VEGF expressing cancer, enabling pancreatic cancer visualization using a NIR intraoperative camera system. We want to test this hypothesis in this pilot intervention study and furthermore we will determine the optimal dosage of bevacizumab- 800CW dosage (4,5 10, 25 or 50mg) to detect pancreatic cancer tissue intraoperatively.

Study objective

Part 1
1. Determine if accumulation of the fluorescent tracer bevacizumab-800CW can be detected for identification of pancreatic cancer tissue during surgery.
2. Identify two doses of conjugate that provide the best visualization of tumor tissue during surgery.
3. 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).

Part 2*
Define which of the two doses of conjugate identified in part 1 is the optimal dose for further development in a phase II/III trial

Study design

This is an interventional exploratory dose escalation trial to be conducted in two trial centers. Studying the fluorescence signal in pancreatic cancer tissue after administration Bevacizumab-800CW 1:2 conjugate (second generation tracer) in patients with clinical suspicion of pancreatic head cancer who are scheduled to undergo surgical intervention with curative intent. The main objective of this study is to determine if accumulation of the fluorescent tracer

bevacizumab-800CW can be detected for the identification of pancreatic cancer tissue during surgery. The secondary objective is to define the optimal dose of the tracer for the visualization of intra operative tumor delineation. For this purpose the study will comprise of 2 parts. In part 1 small cohorts of 3 patients will receive increasing doses of the tracer: 4,5, 10, 25 and 50 mg subsequently. After completion of each cohort efficacy data will be reviewed by determining the fluorescent signal and safety reports. A DSMB is involved to monitor safety and provide advice if the study can proceed to he next dose. In part 1 the two doses with optimal performance will be defined. In part 2 the sample size for the two optimal doses in part 1 will be increased to 10 patients for each of the two dose groups, which is thought to be a sufficient sample size providing a good conclusion with regards to the dose of the tracer that is to be used for further development in a phase III trial.

Intervention

In part one a maximum of 12 patients will receive a single bolus injection of Bevacizumab-800CW three days before surgery. During surgery seven imaging moments are defined in which the near infrared intraoperative camera system will detect the fluorescent signal. The two most optimal dosages will be identified by determining the fluorescent signals. In part two will these two cohorts be extended to ten patients each to define which of the two doses is the optimal dose for further development in a phase II/III trial

Study burden and risks

Risks to study participants are mainly related to the administration of the tracer in increasing dosages. A data safety monitoring board (DSMB) will be installed to carefully monitor safety issues and is authorized to stop the study at any time. Although no specific safety concerns have been raised for the Bevacizumab-800CW conjugate the researches will take into account a possible safety issue which was reported for the Cetuximab-conjugate. A persisting but transient prolongation of QTc was observed in an animal toxicity study (29) and also in the human dose escalation study performed by prof. E. rosenthal. Prof. E. Rosenthal concluded that these side effects were most likely attributable to simultaneous observations of hypomagnesemia, hypocalcemia and hypokalemia which are known side effects of Cetuximab.

The surgical procedure for removal of pancreatic cancer is a very extensive procedure with a high risk of complications. In prior research in the UMCG 30-day mortality rate was 4% (7/176) in patients who underwent a resection. The median intensive care unit stay was 1 day (range 0*73) and median total hospital stay was 24 days (range 9 *131). In the patients who underwent a resection, 29.5% (52/176) had one or more general complications, and 34.1% had a procedure-related complications. 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 160 mg 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 recorded {Starlinger:2012hv}. Since the Bevacizumab-800CW will be used in a dose far below 160mg will therefore cause no additional complication risk.

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 * 18 years.
* Patients with clinical suspicion of pancreatic cancer who are scheduled to undergo surgical intervention with curative intent
* WHO performance score 0-2.
* Signed written informed consent

Exclusion criteria

* Medical or psychiatric conditions that compromise the patient*s ability to give informed consent.
* Other invasive malignancy
* Pregnant or lactating women. Documentation of a negative pregnancy test must be available for woman of childbearing potential. Woman of childbearing potential are pre-menopausal women with intact reproductive organs and women less than two years after menopause.
* Prior neo-adjuvant chemo- of radiotherapy
* 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:	Recruitment stopped
Start date (anticipated):	17-01-2017
Enrollment:	26
Type:	Actual

Medical products/devices used

Generic name:	intraoperative MFRI camera
Registration:	No

Ethics review

Approved WMO Date:	13-01-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-04-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-08-2017
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	EUCTR2015-004247-39-NL
ClinicalTrials.gov	NCT02743975
CCMO	NL50488.042.15