FLuoresence image guided surgery with A VEGF-targeted tracer in soft-tissue Sarcomas in Humans

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Part 11. Determine if accumulation of the fluorescent tracer bevacizumab-800CW can be detected for identification of soft tissue sarcoma during surgery.2. Identify two doses of bevacizumab-800CW that provide the best visualization of tumour tissue...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue neoplasms
Study type	Interventional

Summary

ID

NL-OMON47633

Source
ToetsingOnline

Brief title
Image guided surgery in soft tissue sarcoma (FLASH)

Condition

- Musculoskeletal and connective tissue neoplasms
- Soft tissue neoplasms malignant and unspecified

Synonym
soft tissue sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Surgvision BV,unrestricted grant van

Surgvision

Intervention

Keyword: fluorescence, intraoperative, soft tissue sarcoma, VEGF

Outcome measures

Primary outcome

- Intraoperative assessment of positive margins based on fluorescent images.

- Off table imaging of surgical specimen directly after excision to identify positive margins based on ex vivo fluorescent images.

- Standard histopathological examination to confirm higher fluorescent signals in tumour tissue compared to normal tissue.

- 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 (BlackBox imaging system, Odyssey scanner, fluorescence microscopy).

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

Secondary outcome

Not applicable

Study description

Background summary

There is a need for better visualization of resection margins during surgery for soft tissue sarcomas. Optical molecular imaging of sarcoma associated biomarkers is a promising technique to accommodate this need. The biomarker Vascular Endothelial Growth Factor (VEGF-A) is overexpressed in soft tissue

sarcomas 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 sarcoma visualization using a NIR intraoperative camera system. In this pilot intervention study we will determine the optimal dosage of bevacizumab-800CW (10, 25 or 50mg) to detect soft tissue sarcoma intraoperatively

Study objective

Part 1
1. Determine if accumulation of the fluorescent tracer bevacizumab-800CW can be detected for identification of soft tissue sarcoma during surgery.
2. Identify two doses of bevacizumab-800CW that provide the best visualization of tumour tissue during surgery.
3. 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 Bevacizumab-800CW identified in part 1 is the optimal dose for further development in a phase II trial.

Study design

This is an interventional exploratory dose escalation trial. Studying the fluorescence signal in soft tissue sarcomas after administration of bevacizumab-800CW in patients with clinical suspicion of a soft tissue sarcoma who are scheduled to undergo surgical intervention. The main objective of this study is to determine if accumulation of the fluorescent tracer bevacizumab-800CW can be detected to identify soft tissue sarcoma tissue during surgery. The secondary objective is to define the optimal dose of the tracer to visualize the tumour delineation intraoperatively. For this purpose the study will comprise of two parts. In part 1 small cohorts of three patients will receive increasing doses of the tracer: 10mg, 25mg, and 50mg subsequently. After completion of each cohort efficacy data will be reviewed by determining the fluorescent signal and safety reports. In part 1 the two doses with optimal performance will be defined. In part 2 the sample size for the two doses in part 1 will be increased to 10 patients for each of the two dose groups, to achieve a sufficient sample size to conclusively decide which dose of the tracer has to be used for further development in a phase II trial

Intervention

In part one, a maximum of 9 patients will receive a single bolus injection of bevacizumab-800CW three days before surgery. During surgery three 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 these two cohorts will be extended to ten patients each to define which of the doses is the optimal dose for further development in a phase II trial.

Study burden and risks

Time investment for study participants
Soft tissue sarcoma patients who are scheduled for surgery with curative intent at the UMCG are asked to participate in this trial. Once written informed consent is obtained the patient has one study specific visit for administration of the tracer. In addition to the surgical procedure the study related procedures are expected to take up to 15 minutes extra as compared to regular practice.

Risk for study participants
Risks to study participants are mainly related to the, already present, risks of the surgical procedure and to the administration of the tracer in increasing dosages. A data safety monitoring board (DSMB) will not be installed as in more than 110 patients receiving bevacizumab-800CW, no (serious) adverse events were observed.

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 160mg 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 recorded1. Since the Bevacizumab-800CW will be used in a dose far below 160mg it will therefore cause no additional complication risk, as also evaluated in more than 110 patients after receiving bevacizumab-800CW.

Benefits for study participants
The addition of the near infrared fluorescent imaging agent and camera system during soft tissue sarcoma surgery does not have direct benefits for the participating patients. Interference with standard clinical care is not expected since the surgeons are to follow their normal standard of care during tumour resection surgery. If fluorescent signals are detected during surgery in parts that are not part of the surgical specimen, a maximum of 3 biopsies per fluorescent area may be taken to confirm ex vivo analyses if the fluorescent signals represent cancer tissue.

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 proven soft tissue sarcoma who are scheduled to undergo surgical intervention with curative intent;*- WHO performance score 0-2.

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. ;*- History of infusion reactions to bevacizumab or other monoclonal antibody therapies. ;*- 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):	06-04-2019
Enrollment:	23
Type:	Actual

Medical products/devices used

Generic name:	intraoperative MFRI camera
Registration:	No

Ethics review

Approved WMO Date:	07-09-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	12-06-2018
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	EUCTR2017-001640-35-NL
ClinicalTrials.gov	NCTnognietbekend
CCMO	NL61739.042.17