Detection of pituitary neuroendocrine tumor (PitNET) tissue during endoscopic transsphenoidal surgery using Bevacizumab-800CW: a single center feasibility and dose finding study

Published: 07-01-2020
Last updated: 10-04-2024

The primary objective of this study is to determine the feasibility of intraoperative fluorescence imaging detection of PitNET tissue during TSS using the VEGF-targeting optical agent bevacizumab-800CW in tumors with a Knosp grade of 3 or 4....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON49831

Source
ToetsingOnline

Brief title
DEPARTURE

Condition

- Hypothalamus and pituitary gland disorders
- Endocrine neoplasms benign

Synonym
pituitary adenoma, Pituitary neuroendocrine tumor (PitNET)

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: Bevacizumab-800CW, fluorescence, pituitary neuroendocrine tumor, transsphenoidal surgery

Outcome measures

Primary outcome

- The measured fluorescence intensity that is able to distinguish tumorous from non-tumorous tissue.

- Safety evaluation of vital parameters, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR).

Secondary outcome

- Macroscopic fluorescent signal levels and tracer distribution observed by in vivo NIR fluorescence imaging using the fluorescence endoscopic system.

- Macroscopic fluorescent signal levels and tracer distribution observed by ex vivo NIR fluorescence imaging of the freshly excised specimen directly after excision.

- Intraoperative MDSFR/SFF spectroscopy measurements.

- Fluorescent signal levels on fluorescence images obtained during ex vivo analyses in histological slices

- Standard histopathological examination (H&E staining) to correlate fluorescent signal with histology.

- Histopathological examinations related to ex vivo VEGF expression and

bevacizumab-800CW distribution.

Study description

Background summary

There is a need for improved visualization of presence and extent of pituitary neuroendocrine tumor (PitNET) tissue during transsphenoidal surgery (TSS), especially in tumors invading the cavernous sinus (CS). Optical molecular imaging of PitNET associated biomarkers is a promising technique to accommodate this need. Vascular Endothelial Growth Factor (VEGF-A) is overexpressed in PitNET tissue compared to normal pituitary tissue and has proven to be a valid target for molecular imaging. Bevacizumab is an antibody that binds VEGF-A. By conjugating a fluorescent dye to this antibody, the fluorescent tracer molecule bevacizumab-800CW is created, which binds to VEGF-A. We hypothesize that bevacizumab-800CW accumulates in PitNET tissue, enabling visualization using a molecular fluorescence endoscopy system. In this pilot intervention study we will determine the feasibility of using microdoses (4.5, 10 and 25 mg) of bevacizumab-800CW to detect PitNET tissue intraoperatively. Ultimately, this technique could improve diagnostic accuracy, reduce morbidity in patients with previously unresectable tumors, both preventing unnecessary repeated surgery and additional treatments (radiotherapy and/or medical therapy), allowing major improvements in PitNET management.

Study objective

The primary objective of this study is to determine the feasibility of intraoperative fluorescence imaging detection of PitNET tissue during TSS using the VEGF-targeting optical agent bevacizumab-800CW in tumors with a Knosp grade of 3 or 4.
Secondary objectives are to identify the optimal tracer dose for imaging of PitNET tissue during TSS for further development in a phase II molecular fluorescence endoscopy trial, to quantify fluorescence intensity in vivo and ex vivo with multi-diameter single-fiber reflectance, single-fiber fluorescence (MDSFR-SFF) spectroscopy, to correlate and validate both the in vivo and ex vivo measured fluorescence signals with histopathological analysis and immunohistochemical staining and to assess the (sub)-cellular location of bevacizumab-800CW by ex vivo fluorescence microscopy.

Study design

The study is a non-randomized, non-blinded, prospective, single center, pilot dose-finding study. Nine to fifteen patients with a PitNET with a Knosp grade of 3 or 4 will be included. After inclusion of the first three patients in each

dose group, an interim analysis will be performed to determine tumor-to-background ratios (TBR) by intraoperative fluorescence in vivo measurements incl. MFDSFR/SFF spectroscopy data and by ex vivo back-table fluorescence imaging. After the interim analysis, three scenarios are possible. Optimally, the two most promising groups will be expanded to a total of six patients. If only one dose group allows for differentiation between tumor area and surrounding normal tissue, only this dose will be expanded. If none of the doses show sufficient contract between tumor and normal tissue, the study will be terminated after the interim analysis. In case of the first scenario, expansion of two cohorts, a final analysis will be performed to define the optimal dose, which will represent a balance between the lowest dose and a clinically usable TBR, sufficient to discriminate between tumorous and non-tumorous tissue.

Intervention

Patients will receive a single bolus injection of bevacizumab-800CW (4.5, 10 or 25 mg) two to four days before surgery. During surgery, three imaging moments are defined in which the fluorescence molecular endoscopy system will detect the fluorescent signal.

Study burden and risks

Time investment
Patients with an established diagnosis of PitNET with a Knosp grade of 3 or 4 who are scheduled to undergo TSS 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 15-20 minutes extra compared to regular practice.

Risks
The administration risks of bevacizumab-800CW are reported in the IMPD (version 5.0, November 2017, section 2.4, page 44). No adverse events were reported from previous administrations with bevacizumab-800CW in 187 patients. The endoscopic transsphenoidal procedure for removal of a PitNET is a standard surgical procedure with low morbidity and mortality. Median total hospital stay is 4 to 5 days. (Serious) adverse events occurring in subjects will be recorded until 14 days after tracer administration.

Benefits
Patients will have no benefit from this study directly. Surgery will be planned as usual. Interference with standard clinical care is not expected since the surgeons are to follow their normal standard of care during TSS. During surgery, no additional biopsies will be taken for the study and no decisions will be made based on the fluorescence imaging.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

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 an established diagnosis of PitNET with a Knosp grade of 3 or 4 who are scheduled to undergo TSS.
- WHO performance status 0-2
- Signed written informed consent

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient's ability to give informed consent
- 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):	28-10-2020
Enrollment:	15
Type:	Actual

Medical products/devices used

Generic name:	A clinical therapeutic endoscope;a fiber bundle to perform fluorescence endoscopy and a MDSFR/SFF sp
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO

Date:	07-01-2020
Application type:	First submission

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	27-07-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-09-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-11-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	25-10-2021
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	EUCTR2019-004852-13-NL
ClinicalTrials.gov	NCT04212793
CCMO	NL72459.042.19