Detection of thyroid cancer and central lymph node metastases using bevacizumab-IRDye800CW enhanced Molecular Fluorescence Guided Surgery

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Primary Objectives- To determine the optimal dose of the VEGF-A targeting NIRF tracer bevacizumab-IRDye800CW for an adequate tumor-to-background ratio (TBR) in PTC/FTC/HTC/PDTC lymph node metastases.Secondary Objectives- To evaluate the feasibility…

Ethical review	Approved WMO
Status	Pending
Health condition type	Thyroid gland disorders
Study type	Interventional

Summary

ID

NL-OMON51075

Source
ToetsingOnline

Brief title
TARGET-BEVA

Condition

- Thyroid gland disorders
- Endocrine neoplasms malignant and unspecified

Synonym
thyroid cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: cancer, fluorescence, thyroid cancer, VEGF

Outcome measures

Primary outcome

Primary endpoint

- Fluorescent signal levels defined as Tumor-to-Background Ratio (TBR) derived from PTC/FTC/HTC/PDTC nodal metastasis and normal tissue to determine the optimal dose of Bevacizumab-800CW in patients with PTC/FTC/HTC.

Secondary outcome

Secondary endpoints

- Correlation of the fluorescent signal in PTC/FTC/HTC, nodal metastasis and normal tissue assessed by MFGS with other biological and molecular parameters (IHC) and the fluorescent signal assessed in the ex vivo biopsy specimens.
- Wound bed biopsy specimen characteristics (number of positive and negative biopsies.
- Distribution of bevacizumab-IRDye800CW in PTC/FTC/HTC, lymph nodes and normal tissue as identified by SDS-PAGE and/or ELISA and/or fluorescence microscopy.
- Quantification of sensitivity and specificity of Bevacizumab-800CW in order to make a power size calculation for a possible subsequent diagnostic accuracy study.

Study description

Background summary

Almost 50 % of papillary thyroid cancer (PTC) patients have central lymph node metastases (CLNM), which are associated with a high risk of persistent or recurrent disease. Approximately 5-20% of patients eventually develop loco-regional recurrent disease. However, the practice of performing a prophylactic central lymph node dissection (PCLND) routinely remains controversial. The proponents argue that without a PCLND, PTC patients with positive lymph nodes have an increased risk of local recurrence, and postponed node dissection leads to with 5-6 fold higher risk of morbidity. If performed, PCLND in clinical node negative patients increases staging to pN1 in more than 50% of the cases without increasing survival. To prevent one reoperation, 20 PCLNDs are needed. The complication rate (permanent hypoparathyroidism and recurrent nerve damage) in PCLND is lower when compared to a technically challenging re-exploration in recurrent disease, with reported incidences of 0.6% and 7.3-20%, respectively. Opponents of routine PCLND point out the lack of randomized clinical trials and object to treatment-induced hypoparathyroidism and recurrent nerve damage for the N0 patients. The national protocol in the Netherlands advises based on a very low grade of evidence to perform a CLND in case of males aged over 45 years, large or multifocal tumours, or extra capsular growth. Currently, no diagnostic tool is available which reliably identifies these patient categories. Therefore, there is a clear need for novel diagnostic imaging modalities that overcome this issue. Molecular Fluorescence Guided Surgery (MFGS) is potentially such a diagnostic tool. The administration of NIR fluorescent tracers can increase detection accuracy of cancer and nodal metastatic tissue using macroscopic MFGS. Therefore, we aimed to identify a GMP-produced near infrared (NIR) tracer that potentially has a high target-to-background ratio in PTC compared to normal thyroid tissue. VEGF-A is significantly upregulated at the protein level in PTC compared to normal thyroid tissue. Research showed that VEGF-a is also upregulated in Follicular thyroid carcinoma (FTC), in Hürtle cell carcinoma (HTC) and in Poorly differentiated thyroid carcinoma (PDTC). Clinicians experience the same problem detecting lymph node metastasis in FTC/HTC/PDTC as in PTC. We therefore hypothesize that the GMP-produced NIR-fluorescent tracer bevacizumab-IRDye800CW (targeting VEGF-A, peak emission at 774 nm/789 nm range) might be useful for intraoperative imaging of PTC/FTC/HTC/PDTC and nodal metastases. Our aim is to investigate if the administration of bevacizumab-IRDye800CW is a feasible approach to enable intraoperative selection of PTC/FTC/HTC/PDTC patients for CLND. Eventually, secondary we might also be able to visualize multifocality, more selective lateral neck dissections and asses residual tissue after thyroidectomy. Ultimately, all of these strategies may reduce overtreatment, morbidity, and costs while maintaining the same or better effectiveness with a lower recurrence rate and

improved quality of life.

Study objective

Primary Objectives
- To determine the optimal dose of the VEGF-A targeting NIRF tracer bevacizumab-IRDye800CW for an adequate tumor-to-background ratio (TBR) in PTC/FTC/HTC/PDTC lymph node metastases.

Secondary Objectives
- To evaluate the feasibility of MFGS for the assessment of PTC/FTC/HTC/PDTC and nodal metastasis.
- To correlate and validate fluorescence signals detected in vivo with ex vivo histopathology and immunohistochemistry.
- To evaluate the distribution of bevacizumab-IRDye800CW on a microscopic level.
- To quantify sensitivity and specificity of bevacizumab-IRDye800CW for PTC/FTC/HTC/PDTC and nodal metastasis in order to make a power size calculation for a possible subsequent diagnostic accuracy study

Study design

The TARGET-BEVA study is a non-randomized, non-blinded, prospective, single center phase I feasibility study for patients with TxNxM0 confirmed PTC/FTC/HTC/PDTC, for which we will determine the dosage group with the best TBR in PTC/FTC/HTC/PDTC nodal metastasis. We will initiate the phase I study with a 2 x 3 scheme: 10 mg (n=3 with confirmed lymph node metastasis), and 25 mg (n=3 with confirmed lymph node metastasis). We will start with a dosage group of 10 mg, and increase to a dosage of 25 mg. Dosages are based on data from previous studies performed in our center showing that the administration of these doses in patients with solid tumors is safe and provides a good TBR. As the primary objective is the detection of lymph node metastasis, we will perform a dose finding study and will only proceed to the next dosage group if we can determine a TBR in three patients. The reasoning for this approach is the low sensitivity of preoperative imaging for lymph node metastasis. Metastasis can only be confirmed after histopathological examination. Following completion of the dosage groups an interim analysis will be performed to assess the dosage that will provide the optimal TBR in nodal metastasis. We will analyze the TBR for each dosing group. The TBR will be calculated as follows: TBR = (tumor fluorescence)/(surrounding tissue fluorescence). If both dosage cohort provide the same excellent TBR, we will deescalate to a dosage of 4.5 mg (n=3 with confirmed lymph node metastasis) to evaluate TBR and reduce possible tracer toxicity. Finally, for the dosage cohort with the most optimal TBR we will expand this group to a total of ten patients to have a minimal significant data set which will serve for a subsequent accuracy study. Should the safety profile or dosage in terms of optimal TBR not be sufficient, we abandon the tested tracer.

Intervention

Tracer administration: Bevacizumab-800CW is administered via an IV 2 days before surgery and patients are monitored for any
to be able to observe side effects. Dosages of 4.5 / 10 / 25mg can be used in this study.

Specimen-related study protocol: The excised tissue is examined histopathologically according to current
protocols for clinical oncology care. Diagnosis, tumor size, multifocality, margins and histological features
The pathologist reports on clinical decision-making. In addition, ex vivo is taken outside of the operating room for
fluorescent imaging. This data is related to histopathological data (H&E and additional immunohistochemical stains such as VEGF-A) and the localization of the fluorescent lesions.

Study burden and risks

Patient and specimen related protocols
Tracer administration: Bevacizumab-IRDye800CW will be administered two days prior to incision by infusion and/or bolus injection. Patients will be monitored for 15 minutes for potential side effects. Dosages administered throughout the study will be either 4.5 mg, 10 mg and 25 mg.
Perioperative imaging: The aim is to test the accuracy of bevacizumab-IRDye800CW (TBR) to primary identify PTC/FTC/HTC/PDTC nodal metastases. A multispectral Near Infrared Fluorescence (NIRF) camera system sensitive for bevacizumab-IRDye800CW fluorescence will be used for intraoperative imaging of the lymph node dissection. During the procedure, the surgeon may take a maximum of ten additional biopsies from regions of interest to acquire information about tracer accuracy (for example fluorescent positive tissue macroscopically not suspect as malignant tissue or fluorescent negative tissue that macroscopically is suspected to be malignant tissue). Finally, the excised specimens will be imaged ex vivo to acquire additional information about fluorescence distribution. This phase 1 study procedures will not influence surgical decision making nor the extend of surgery. General clinical practice will have priority over study procedures. Histopathological features of all excised tissue will be assessed by a pathologist.
Specimen related study protocol: The excised specimens will undergo histopathological assessment according to the current standard used in clinical cancer care. Diagnosis, tumor size, multi-focality, margins and selected histological features necessary for clinical decision making will be provided by the pathologist. Next to this, ex vivo imaging will be performed on the excised specimen and biopsies. In vivo and ex vivo images will be related to histopathological data (H&E and additional immunohistochemical stainings such

as VEGF-A) and the location of the fluorescent lesions.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Age >= 18 years, eligible for surgery
2) Bethesda VI fine needle aspiration (FNA) thyroid or FNA proven PTC/FTC/HTC/PDTC metastasis (primary or recurrence).
3) Scheduled to undergo central and/or lateral lymph node dissection with or without thyroidectomy as discussed in the Multi-Disciplinary Thyroid Board.
4) WHO performance score of 0-2.
5) Written informed consent.
6) Mentally competent person who is able and willing to comply with study procedures.

7) For female subjects who are of childbearing potential are premenopausal with intact reproductive organs or are less than two years post-menopausal:
o A negative serum pregnancy test prior to receiving the tracer
o Willing to ensure that she or her partner uses effective contraception during the trial and for 3 months thereafter.

Exclusion criteria

1) Pregnancy or breast feeding
2) Advanced stage thyroid cancer not suitable for surgical resection
3) Medical or psychiatric conditions that compromise the patient*s ability to give informed consent
4) Concurrent anticancer therapy (chemotherapy, radiotherapy, vaccines, immunotherapy) delivered within the last three months prior to the start of the treatment
5) The subject has been included previously in this study or has been injected with another investigational medicinal product within the past six months
6) History of myocardial infarction (MI), TIA, CVA, pulmonary embolism, uncontrolled congestive heart failure (CHF), significant liver disease, unstable angina within 6 months prior to enrollment
7) Any significant change in their regular prescription or non-prescription medication between 14 days and 1 day prior to IMP administration.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-08-2021
Enrollment:	32
Type:	Anticipated

Ethics review

Approved WMO Date:	16-09-2021
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	EUCTR2021-001215-84-NL
CCMO	NL77079.042.21