Detection of Lymph Node Metastases in Papillary Thyroid Cancer using EMI-137 enhanced Molecular Fluorescent Guided Imaging: a multicentre feasibility and safety study

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2.1 Primary Objective- To determine the optimal dose of the c-Met targeting NIRF tracer EMI-137 for an adequate tumor-to-background ratio (TBR) in PTC lymph node metastases.2.2 Secondary Objectives- To obtain information on safety aspects of...

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

Summary

ID

NL-OMON48718

Source
ToetsingOnline

Brief title
Thyroid TARGET study

Condition

- Thyroid gland disorders
- Endocrine neoplasms malignant and unspecified
- Endocrine gland therapeutic procedures

Synonym
Papillary thyroid carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Healthy Aging UMCG / KWF Grant

Intervention

Keyword: cancer, cmet, fluorescence, papillary thyroid cancer

Outcome measures

Primary outcome

- Fluorescent signal levels defined as Tumor-to-Background Ratio (TBR) derived from PTC nodal metastasis and normal tissue.

Secondary outcome

- Number of (severe) adverse events (SAE/AEs).

- Correlation of the ex-vivo fluorescent signal in PTC, nodal metastasis and normal tissue with other biological and molecular parameters (IHC).

- Macroscopic and real-time quantification of the fluorescent signal of pathological confirmed PTC, nodal metastasis and normal tissue observed by means of the MDSFR/SFF spectroscopy probe (M/m3).

- Distribution of EMI-137 in PTC, lymph nodes and normal tissue as identified by SDS-PAGE and/or ELISA and/or fluorescence microscopy.

- Comparison between the amount of nodal metastasis found with preoperative imaging and the amount of nodal metastasis identified based on fluorescence signals.

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 hypo-parathyroidism 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 hypo-parathyroidism 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 yrs, 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 Imaging (MFGI) is potentially such a diagnostic tool. The administration of NIR fluorescent tracers can increase detection accuracy of cancer and nodal metastatic tissue using macroscopic MFGI. 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. Tyrosine-protein kinase Met (c-Met) is significantly upregulated at the protein level in PTC compared to normal thyroid tissue. We therefore hypothesize that the GMP-produced NIR-fluorescent tracer EMI-137 (targeting c-Met, peak emission at 675 nm range) might be useful for imaging of PTC and nodal metastases. Our aim is to investigate if the administration of EMI-137 is a feasible approach to enable detection of PTC and nodal metastases. Eventually, 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

2.1 Primary Objective
- To determine the optimal dose of the c-Met targeting NIRF tracer EMI-137 for

an adequate tumor-to-background ratio (TBR) in PTC lymph node metastases.

2.2 Secondary Objectives
- To obtain information on safety aspects of administration by registration of conjugate integrity, side effects, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR).
- To determine the feasibility of ex-vivo spectroscopy measurements of PTC and lymph nodes for quantification of the fluorescence signal of EMI-137.
- To correlate and validate ex-vivo fluorescence signals with histopathology and immunohistochemistry.
- To evaluate the distribution of EMI-137 on a microscopic level.
- To quantify sensitivity and specificity of EMI-137 for PTC and nodal metastasis in order to make a power size calculation for a possible subsequent diagnostic accuracy study.
- To correlate the combined results of histopathology and ex-vivo fluorescence imaging with preoperative imaging results.

Study design

The study is designed as a Phase I study for patients with confirmed PTC, for which we will determine a safety profile of the c-Met targeted tracer according to Common Terminology Criteria for Adverse Events (CTC) 5.0 criteria by implementing a dose-finding method. Additionally, we will perform ex vivo fluorescence imaging (white-light (WL), fluorescence (FL), overlay) and spectroscopy of the thyroid gland, lymph node metastases and normal tissue at predefined time-points. The aim is to identify the dosage group with the best tumor-to-background ratio (TBR) in lymph node metastasis. Based on an earlier NIR fluorescence endoscopy study using the same tracer EMI-137 (targeting c-Met), we will start the Phase I study with a classical 4x3 scheme. 0.045 mg/kg (n=3), 0.09 mg/kg (n=3), 0.13 mg/kg (n=3), and 0.18 mg/kg (n=3). We will start with the dosing 0.09 mg/kg, increase to 0.13 mg/kg and finish with a dosage of 0.18 mg/kg. Following completion of all dosage groups an interim analysis will be performed to assess safety and the dosage that provides the optimal TBR in nodal metastasis. A maximum concentration level of 0.18 mg/kg is accepted as the upper limit, as patients with PTC have an excellent long-term prognosis. A dose limiting toxicity (DLT) of one per group is accepted. After obtaining the safety profile of all three dosing groups, we will then analyze the TBR for each dosing group. The TBR will be calculated as follows: TBR = (tumor fluorescence)/(surrounding tissue fluorescence). Should the 0.09 mg/kg group have an excellent TBR we will deescalate back to a 0.045 mg/kg group (n=3) to evaluate TBR and reduce possible tracer toxicity. If the TBR difference between dosage groups is not sufficient, the dosage groups can be extended with 3 additional patients per group followed by an interim analysis. Finally, for the dosing cohort with the most optimal TBR we will expand this group to a total of 10 patients to have a minimal significant data set which will serve for a subsequent diagnostic accuracy study. If two dosing groups have a similar TBR as calculated from the second interim analysis, both dosage

groups can be extended to a total of 10 patients. Should the safety profile or dosage in terms of optimal TBR not be sufficient, we abandon the tested tracer.

Intervention

Tracer administration: EMI-137 will be administered 2 hours prior to incision by infusion and patients will be monitored for potential side effects. Dosages administered throughout the study will be either 0.045, 0.09, 0.13 or 0.18 mg/kg.

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 and spectroscopy will be performed on the excised specimen. Ex vivo fluorescence images and spectroscopy data will be related to histopathological data (H&E and additional immunohistochemical stainings such as c-Met) and the location of the fluorescent lesions.

Study burden and risks

Burden-extra procedures: 1) Intravenous administration of EMI-137

Risks: None of the preclinical toxicology and safety pharmacology studies performed with EMI-137 identified any specific adverse safety signals relevant to the injection of EMI-137 in humans. A possible SAE for injection of EMI-137 could be an allergic and/or anaphylactic reaction, therefore a crash cart with medication to convert an anaphylactic reaction will be present at the site of the injection.

Benefit: Patients will have no direct benefit from this study. Surgery will be planned as usual. During surgery, no decisions will be made based on the fluorescence imaging. The benefit of this study will be the assessment of safety and the establishment of usefulness of EMI-137 during surgery to identify PTC and central lymph node metastases. Clinical experience will be obtained with fluorescent labeled tracers during surgery PTC. The results of these types of study will be at least beneficial for other patients with cancer in the future.

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

1. Age * 18 years, eligible for surgery
2. Bethesda VI fine needle aspiration (FNA) thyroid or FNA proven PTC 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:
- A negative serum pregnancy test prior to receiving the tracer
- 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:	Recruitment stopped
Start date (anticipated):	20-06-2018
Enrollment:	32
Type:	Actual

Ethics review

Approved WMO Date:	06-12-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-02-2018

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	13-04-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	31-05-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-10-2019
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	EUCTR2017-003175-56-NL
ClinicalTrials.gov	NCT03470259
CCMO	NL62817.042.17