Reinducing radioiodine-sensitivity in radioiodine-refractory thyroid cancer using lenvatinib

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Determine the fraction of RAI-R thyroid cancer patients who are eligible for I-131 therapy after 6- or 12-week lenvatinib treatment to an extent that clinically meaningful tumour radiation doses [Gy] can be safely delivered with acceptable I-131...

Ethical review	Approved WMO
Status	Completed
Health condition type	Endocrine neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55301

Source
ToetsingOnline

Brief title
RESET

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
Radioiodine-refractory thyroid cancer, radioiodine-resistant thyroid cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: dosimetry, radioactive iodide, radioiodine-refractory thyroid cancer, redifferentiation

Outcome measures

Primary outcome

Fraction of RAI-R thyroid cancer patients who are eligible for I-131 therapy after 6- or 12-week lenvatinib treatment to an extent that clinically meaningful tumour radiation doses [Gy] can be safely delivered with acceptable I-131 activities [MBq] as determined by I-124 dosimetry of both lesions and healthy organs at risk.

Secondary outcome

• Extent of RAI uptake and retention at baseline and after 6- or 12-week lenvatinib

• Optimal duration of lenvatinib treatment (6 weeks or 12 weeks) for maximum redifferentiation to occur.

• Agreement between expected absorbed dose per lesion predicted by I-124 PET/CT dosimetry and actual absorbed dose per lesion determined by intra-therapeutic I-131 SPECT/CT dosimetry in patients in which I-131 therapy is warranted.

• Metabolic and biochemical treatment response using F-18 FDG PET and unstimulated (TSH-suppressed) thyroglobulin levels, respectively.

• Overall survival, best objective response and progression free survival.

• Incidence and severity of toxicities according to CTCAE 5.0.

• Quality of life

An explorative endpoint of this study is to evaluate alterations at the transcriptional and translational level in biopted tumour lesions before and after lenvatinib treatment and to determine whether treatment response is related to genetical profiles.

Study description

Background summary

Radioactive I-131 therapy is a mainstay therapy in advanced differentiated thyroid cancer (DTC), thereby offering substantial survival and palliative benefits to the patient. Its effectiveness is correlated with the ability of cancer tissue to take up and retain radioiodine (RAI) after which the tissue*s structure is damaged by the emission of short-pathlength beta particles. The sodium iodide symporter (NIS) plays a pivotal role in the uptake and retention of RAI. About two-third of patients with distant metastases will develop RAI-refractory (RAI-R) thyroid cancer, characterized by an affected expression of NIS and poor response to I-131 therapy or patients reaching the maximum recommended cumulative dose of more than 22.2 GBq. Management of these patients is a considerable challenge in clinical practice and the disease is therefore associated with a poor overall prognosis. Currently, multi-tyrosine kinase inhibitors (TKIs) like lenvatinib and sorafenib are recommended treatment options of progressive, locally advanced or metastasized RAI-R DTC, but have variable side-effects and a modest effect on progression-free survival.

A potential alternative way to achieve disease control in RAI-R thyroid cancer is to re-sensitize tumours to RAI using redifferentiation agents such as multi-tyrosine kinase inhibitors (TKIs) like lenvatinib and subsequently employ RAI therapy. The direct antitumour activity of these multikinase inhibitors is based on the inhibition of angiogenesis and cell growth via molecular pathways that are also involved in the regulation of NIS. The ability to enhance RAI uptake and retention has already been observed for TKIs selumetinib, vemurafenib and dabrafenib. In contrast, sorafenib showed disappointing results regarding renewed RAI uptake and retention. In this pilot study, we will evaluate the ability of lenvatinib to increase NIS expression and RAI uptake and retention to halt resistance to I-131 therapy in RAI-R thyroid cancer.

Study objective

Determine the fraction of RAI-R thyroid cancer patients who are eligible for I-131 therapy after 6- or 12-week lenvatinib treatment to an extent that

clinically meaningful tumour radiation doses [Gy] can be safely delivered with acceptable I-131 activities [MBq] as determined by I-124 dosimetry of both lesions and healthy organs at risk.

Study design

This is a single-centre open label phase II study evaluating the effect of lenvatinib treatment for restoring radioiodine uptake and retention in RAI-R thyroid cancer to warrant I-131 therapy. RAI-R DTC patients starting standard-of-care lenvatinib treatment will be included in this study. Prior to lenvatinib treatment, patients will undergo I-124 PET/CT to quantify RAI uptake and retention at baseline. Besides that, patients undergo F-18 FDG PET/CT and a biopsy is performed. An additional biopsy is performed after 6 weeks of lenvatinib treatment. The first half of the intended sample size (cohort 1) will be treated with lenvatinib for a total of 12 weeks. After 6- and 12-week treatment, patients will undergo I-124 PET/CT dosimetry to evaluate the redifferentiation effect and to assess expected absorbed lesion doses and the MTA. Patients will undergo subsequent I-131 therapy if a clinically meaningful lesion dose is expected with the MTA of I-131. For all patients eligible for I-131 therapy, lenvatinib is discontinued prior to administration of I-131 and post-therapeutic I-131 SPECT dosimetry will be performed for dose verification. Results between 6- and 12-week lenvatinib treatment will be compared to select the lenvatinib treatment duration that leads to highest extent of redifferentiation. The next patients (cohort 2) will then receive lenvatinib for either 6 or 12 weeks. Patients who are not eligible for I-131 therapy, will continue lenvatinib treatment at the discretion of the treating physician. Patients will be followed up according to current guidelines for a total of 9 months after the start of lenvatinib treatment. Metabolic and biochemical response will be assessed using F-18 FDG PET/CT and Tg levels, respectively.

Intervention

I-124 dosimetry

Study burden and risks

Patients who will be included in this study have advanced thyroid cancer with poor prognosis and a lack of effective treatment options. Although RAI-R thyroid cancer may show slow progression in the beginning of disease, the progression accelerates towards the end of disease. Therefore, most of these patients are showing a high disease-related mortality. Short-course treatment with lenvatinib is expected to redifferentiate RAI-R thyroid cancer to an extent that I-131 therapy becomes feasible in 60% of patients. There is a common agreement among leading physicians that redifferentiation is the best option for RAI-R DTC patients which has been published in several peer-reviewed

reviews and articles. Additionally, the dosimetry approach used in this study is going to prevent patients who are not likely to benefit from I-131 therapy from palliative treatment with high activities of RAI. Determining the MTA in patients will avoid life-threatening side-effects of I-131 therapy, which is still not taken into account in administering an activity following the current empirical approach. Since most patients already had several I-131 treatments, the cumulative radiation-related toxicities become of importance. Investigating the extent of redifferentiation after lenvatinib treatment, i.e. increased or renewed RAI uptake and retention, and determining the effective and safe I-131 activity that can be administered to the patient comes at the cost of additional 6-14 blood drawings and whole body counting procedures, 2-3 administrations of I-124, up to 2 administrations of F-18 FDG and a total of 5-7 PET/CT scans (instead of routinely performed contrast-enhanced whole body CT scans every 12 weeks). Additionally, an extra biopsy is performed during lenvatinib treatment. To verify the delivery of I-131 to lesions and critical structures, a total of 3 post-therapeutic SPECT/CT scans will be performed which requires only one extra visit to the hospital as patients are expected to have a mandatory hospital admission of 4-5 days after I-131 administration.

We believe that the advantages significantly outweigh the additional visits to the hospital to undergo these scans (with accompanying radiation burden), blood drawings, whole-body retention measurements and the biopsy. A substantial amount of patients is likely to benefit from this study, at least to slow down tumour progression significantly. The major risk for patients in this study lies in the medication. Lenvatinib is well known to have side effects. As we aim to apply short-term treatment of either 6 or 12 weeks, the toxicity burden to patients is expected to be reduced in comparison to standard-of-care long-term lenvatinib treatment. Since most of the side effects are reversible, we do not expect severe side effects which cannot be treated symptomatically or locally during short-term lenvatinib treatment. No cumulative toxicities have been described by the sequential combination of short-term application of other TKIs and RAI.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Age >= 18 years at the time of informed consent
• Histologically or cytologically confirmed DTC (including papillary, follicular or Hürthle Cell carcinoma)
• Progressive (biochemical or anatomic) disease for which lenvatinib is started as standard treatment at the discretion of the treating physician.
• Measurable disease at baseline imaging (F-18 FDG PET) according to the definition of the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) 1.0 with at least one lesion >=1.0 cm in the longest diameter for a non-lymph node or >=1.5 cm in the short axis for a lymph node.
• RAI-R disease on structural imaging, defined as any one of the following:
o Metastatic lesions that are not RAI-avid on a diagnostic or intra-therapeutic RAI scan performed prior to enrolment in the current study
o RAI-avid metastatic lesions which remained stable in size or progressed according to RECIST 1.1 criteria despite RAI treatment. Absence of response is observed during 6-9 months after high dose I-131 therapy.
• No recent treatment for thyroid cancer:
o No prior I-131 therapy is allowed <6 months prior to initiation of therapy on this protocol (a diagnostic study using <400 MBq of I-131 is not considered 131I therapy)
o No external beam radiation therapy is allowed <4 weeks prior to initiation of therapy on this protocol. (Previous treatment with radiation for any indication is allowed if the investigator judges that the previous radiation does not

significantly compromise patient safety on this protocol)
• Eastern Cooperative Oncology Group (ECOG) performance status <=2 (or Karnofsky >=60%)
• Life expectancy >=3 months
• Ability to swallow and retain orally-administered medication and no clinically significant gastrointestinal abnormalities that may alter absorption
• Creatinine <=1.5 mg/dL (<=133 µmol/L) or estimated glomerular filtration rate (eGFR) (using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) >=50 mL/min/1.73m2 or 24-hour urine creatinine clearance >=50 mL/min/1.73m2
• Adequate blood coagulation function as evidenced by an international normalized ratio (INR) <=1.5
• Adequate bone marrow function with:
o Absolute neutrophil count >=1.5 * 10^9/L
o Hemoglobin >=9 g/dL (5.6 mmol/L)
o Platelets >=100 *10^9/L
• Adequate liver function with
o Albumin >=25 g/L
o Total bilirubin <1.5x institutional upper limit of normal (ULN) with an exception for patients with Gilbert*s syndrome
o Aspartate aminotransferase and alanine aminotransferase <=3x institutional ULN (<=5x ULN if subject has liver metastases)
• Negative pregnancy test within 7 days prior to starting the study for premenopausal women. Women can be included without pregnancy test if they are either surgically sterile or have been post-menopausal for >=1 year.
• Sexually active women of childbearing potential must agree to use a highly effective method of contraception during the study and for at least 6 months after the last study treatment administration. Sexually active males patients must agree to use condom during the study and for at least 6 months after the last study treatment administration. Also, it is recommended their women of childbearing potential partner use a highly effective method of contraception. Effective methods of contraception are defined as those, which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly (for example implants, injectables, combined oral contraception or intra-uterine devices). At the discretion of the investigator, acceptable methods of contraception may include total abstinence in cases where the lifestyle of the patient ensures compliance. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable methods of contraception.)
• Voluntary agreement to provide written informed consent and the willingness and ability to comply with all aspects of the protocol

Exclusion criteria

• Concomitant or previous malignancies within the last 3 years. Patients are

eligible for this study if they have been disease-free of the previous malignancy for at least 3 years, have a history of completely resected non-melanoma skin cancer and/or have indolent secondary malignancies.
• Symptomatic or untreated leptomeningeal or brain metastases or spinal cord compression
• Evidence of cardiovascular risk including any of the following:
o Clinically relevant arrhythmias
o Acute coronary syndromes, severe/unstable angina
o Symptomatic congestive heart failure
• Use of other investigational drugs within 28 days preceding the first dose of treatment in this study or during the study
• Have a known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to lenvatinib and/or to Thyrotropin alfa (human recombinant thyrotropin)
or other known contents of the two drugs.
• Inability to follow a low iodine diet or requiring medication with high content in iodide (e.g. amiodarone)
• Patients who received iodinated intravenous contrast as part of a radiographic procedure within 6-8 weeks of study registration. Patients are eligible for this study if urinary iodine analysis reveals that the excess iodine has been adequately cleared after the last intravenous contrast administration
• Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or psychiatric illness/social situations that would limit compliance with study requirements.
• Pregnant, lactating or breast feeding women
• Any medical or other condition that in the opinion of the investigator(s) would preclude the participation in a clinical study
• Unwillingness or inability to comply with study and follow-up procedures.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	12-01-2022
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	09-02-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL75169.058.20