Intra-arterial Lutetium-177- dotatate for treatment of patients with neuroendocrine tumor liver metastases

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To investigate the impact of intra-arterial administration of 177Lu-dotatate on the intrahepatic biodistribution in patients with NET liver metastases. Our primary objective is to to evaluate if there is a difference in post-treatment tumor-to-non-...

Ethical review	Approved WMO
Status	Completed
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49314

Source
ToetsingOnline

Brief title
LUTIA

Condition

- Other condition
- Malignant and unspecified neoplasms gastrointestinal NEC
- Metastases

Synonym
liver metastases, NET, neuroendocrine tumors

Health condition

neuroendocriene tumoren (graad I&II)

Research involving

Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,Advanced Accelerator Applications

Intervention

Keyword: Intra-arterial, Liver metastases, Lutetium, Neuroeindocrine

Outcome measures

Primary outcome

To assess if there is a difference in post-treatment tumor-to-non-tumor (T/N) activity concentration ratio on SPECT/CT between the intra-arterial treated liver lobe and the intravenous treated liver lobe. The T/N activity concentration will be measured on SPECT/CT. The primary endpoint will be assessed after the first treatment cycle. The T/N activity ratios of the second, third, and final treatment cycle will be assessed as secondary endpoint. Tumor response, toxicity, extrahepatic uptake and kidney uptake are secondary endpoints. Intra- and inter-patient differences will be studied.

Secondary outcome

- There is a difference in absolute values of mean tumor and healthy liver absorbed dose on post-treatment SPECT/CT between the intra-arterial treated liver lobe and the intravenous treated liver lobe?
- There is a difference in post-treatment tumor response between the intra-arterial treated liver lobe and the intravenous treated liver lobe?
- There is a dose-response relation between tumor absorbed dose and post-treatment tumor response?

- There is toxicity and how toxicity is compared to historical controls?

- There is sufficient uptake of 177Lu-dotatate in extrahepatic lesions?

- There is sufficient uptake of 177Lu-dotatate in the contralateral lobe,

compared to historical controls?

- There is a difference in kidney uptake of 177Lu-dotate between the IA treated

patients and historical controls?

- There is a difference in T/N activity concentration ratio between different

timepoints post-injection?

Study description

Background summary

The majority of neuroendocrine tumor (NET) patients present with metastases, most often including liver metastases. These patients have a poorer prognosis and lower quality of life.
Currently, intravenous administered somatostatin-bound radionuclides (177Lu-dotatate) have shown to improve tumor response rates and progression free survival (PFS). Despite of the increased tumor response rate and PFS, liver metastases still remain the major cause of morbidity and mortality in these patients. Patients with liver metastases have a worse outcome in terms of overall survival after treatment with 177Lu-dotatate compared to patients with limited or no liver metastases.

Study objective

To investigate the impact of intra-arterial administration of 177Lu-dotatate on the intrahepatic biodistribution in patients with NET liver metastases. Our primary objective is to to evaluate if there is a difference in post-treatment tumor-to-non-tumor (T/N) activity concentration ratio on SPECT/CT between the intra-arterial treated liver lobe and the intravenous treated liver lobe.

Study design

Multicenter, interventional, block randomized, phase 2 clinical trial. We use a within-subject controlled design where the administration of 177Lu-dotatate is randomized between the right or left hepatic artery. Selective IA

administration of 177Lu-dotatate allows for intra-patient comparison between IA administration (one lobe) versus IV *administration* (the other lobe). The contralateral liver lobe and the rest of the body receive treatment by second pass IV route.
A subset of included patients will be scanned using SPECT/CT and total-body scans at multiple time-points post-injection to allow for comparison of uptake ratio*s at different time points and mean absorbed dose calculations. SPECT/CT allows for mean absorbed dose calculation in liver tumors and healthy liver tissue, while total-body imaging evaluates kinetics in extra-hepatic lesions.
The subset of patients will receive a total of 4 SPECT/CT*s and 4 total-body acquisitions after their first treatment to evaluate pharmacokinetic properties of 177Lu-dotatate after intra-arterial injection. The four time points are *-1, 4-5, 24±3 and 168±24 hours after administration of 177Lu-dotatate. Each patient who is eligible for the study, could optionally participate in the sub-study.

Intervention

Treatment will be randomized between selective right or left hepatic artery administration of 177Lu-dotatate (Four administrations of 7.4 GBq; each via the same randomly allocated hepatic artery during angiography).

Study burden and risks

As with the standard IV treatment with 177Lu-dotatate, the treatment consists of four cycles. During each cycle, patients will be admitted for 1 night and undergo physical examination, laboratory examination, angiography with administration of the treatment dose, and post-treatment imaging. Risks include standard complication risks related to angiography (bleeding or infection). No additional risks with relation to the treatment itself are expected compared to the standard IV treatment (nausea, vomiting).

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584 CX

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Patients must have given written informed consent.
- Female or male aged 18 years and over.
- Inoperable histologically proven neuro-endocrine tumor with indication for 177Lu-dotatate at enrollment time.
- Well-differentiated neuro-endocrine tumor with a Ki67-index <=20% and a mitotic count of <=20.
- Confirmed presence of somatostatin receptors on target lesions, based on somatostatin receptor imaging.
- Life expectancy of 6 months or longer.
- Eastern Cooperative Oncology Group (ECOG) performance score 0-1.
- Hepatic metastases with at least one lesion >=3 cm on cross sectional imaging in both the right and left liver lobe (i.e. left and right lobes are based on the hepatic arterial perfusion territory).
- Presence of excessive liver metastases, defined as >25% tumor load.
- Patients may or may not have extrahepatic metastases.
- Patients must have clinical or radiological progressive disease.
- Negative pregnancy test for women of childbearing potential.

Exclusion criteria

- Any previous radioembolization, chemoembolization, or bland embolization, at any time, or surgery or radiofrequency ablation (or other ablative therapies) within 12 weeks prior to randomization in the study.
- Prior external beam radiation therapy to the liver.
- Interferons, Everolimus (mTOR-inhibitors) or other systemic therapies within 4 weeks prior

to randomization in the study.
- Any patient receiving treatment with short-acting Octreotide, which cannot be interrupted for 24 hours before and 24 hours after the administration of 177Lu-dotatate, or any patient receiving treatment with Octreotide LAR, which cannot be interrupted for at least 4 weeks before the administration of 177Lu-dotatate, unless the tumor uptake on target lesions observed by imaging during continued Octreotide LAR treatment is higher than normal liver uptake.
- Any unresolved toxicity greater than National Cancer Institute (NCI), Common Terminology Criteria for Adverse Events (CTCAE version 4.03) grade 2 from previous anti-cancer therapy.
- Serum bilirubin > Upper Limit of Normal (ULN), serum albumin <3.0 g/dL.
- Glomerular filtration rate <50 ml/min.
- Hb <5.5 mmol/L; leucocytes <3.0x109/L; platelets <100x109/L (at baseline; 75x109/L is sufficient for cycles 2-4).
- Uncontrolled congestive heart failure (NYHA II, III, IV).
- Uncontrolled diabetes mellitus.
- Patients suffering from diseases with an increased chance of liver toxicity.
- Patients suffering from psychic disorders that make a comprehensive judgement impossible, such as psychosis, hallucinations and/or depression. Patients who are declared incompetent.
- Previous enrolment in the present study or previous treatment with 177Lu-dotatate.
- Female patients who are not using an acceptable method of contraception (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation) OR are less than 1 year postmenopausal or surgically sterile during their participation in this study (from the time they sign the consent form) to prevent pregnancy.
- Male patients who are not surgically sterile or do not use an acceptable method of contraception during their participation in this study (from the time they sign the consent form) to prevent pregnancy in a partner.
- Body weight over 150 kg.
- Current spontaneous urinary incontinence.
- Severe allergy for i.v. contrast (Visipaque®), used for CT evaluation and treatment angiography.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	10-08-2018
Enrollment:	26
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Lutathera
Generic name:	Lutetium-177-dotatate

Ethics review

Approved WMO Date:	25-06-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-06-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-05-2019
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-000369-54-NL
ClinicalTrials.gov	NCT03590119
CCMO	NL60725.041.17

Study results

Date completed: 27-01-2023

Results posted: 21-11-2023

First publication
28-10-2023