Phase I clinical trial using a novel CCK-2/gastrin receptor-localizing radiolabelled peptide probe for personalized diagnosis and therapy of patients with progressive or metastatic medullary thyroid carcinoma

Published: 25-04-2016
Last updated: 20-04-2024

Primary Objectives1. to establish the safety of intravenous administration of a therapeutic peptideamount of the CP042. to assess the biodistribution and dosimetry of 111In-CP04 in cancer and normal tissues and to determine critical organs.Secondary...

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

Summary

ID

NL-OMON46298

Source
ToetsingOnline

Brief title
GRAN-T-MTC

Condition

- Endocrine neoplasms malignant and unspecified

Synonym
medullary thyroid cancer, medullary thyroid carcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Azienda Ospedaliero-Universitaria Pisana
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CCK-2, Gastrin, Medullary Thyroid Carcinoma, MTC

Outcome measures

Primary outcome

Outcome measures

1. Safety of intravenous administration of CP04 at low-dose (diagnostic amount) and high-dose (therapeutic amount) peptide radiolabelled with 200±10% MBq of 111In (diagnostic amount) will be assessed by type, frequency, severity, timing and relation to the studied radiopharmaceutical administration of adverse events and laboratory abnormalities based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0

2. Biodistribution and pharmacokinetics\for target lesion and for discernible organs will be evaluated from sequential planar images. Calculation of the residence time of 111In in discernible thoracic and abdominal organs, target lesion and blood will be performed and organ as well as tumour doses (mGy/MBq) calculated. These data will provide all required data for evaluation of the feasibility of a therapeutic application of CP04.

3. Diagnostic sensitivity/specificity of 111In CP04 to detect cancer lesions for both diagnostic and therapeutic peptide amount by Qualitative Visual Analysis (number of patients with uptake at site of lesion, the number of

lesions with abnormal tracer uptake at scintigraphy, the number and site of lesions with pathological uptake detected per verifiable organ or body region relative to those detected by conventional imaging)

4. Influence of a diagnostic amount of CP04 peptide vs. a therapeutic amount of peptide on tumour and organ uptake, the identification of the time points post-injection with the highest observed number of lesions and the highest tumour/background ratios will be performed.

5. The relative decrease of kidney adsorbed dose after co-administration of Gelofusine.

Secondary outcome

Not applicable

Study description

Background summary

Medullary thyroid carcinoma (MTC) is still one of the most challenging cancers for both physicians and patients [1-4]. Epidemiological studies have shown that during the past 30 years neither a change in stage at diagnosis nor improvement in survival has occurred for MTC patients [5, 6].
Patients with metastatic MTC are left with few inefficient therapeutic options. Therefore, it is necessary to develop alternative therapeutic strategies to control tumour growth. The cholecystokinin 2 (CCK-2) receptor is overexpressed in MTC with very high density and incidence of over 90%, as revealed by autoradiographic studies. From the late 1990*s, a variety of CCK-2/gastrin related peptides (members of the gastrin- and cholecystokinin families, or possessing characteristics of both), were studied in vitro and in preclinical animal models. In a comparison study performed within COST BM0607 (previous collaboration of the investigators under supervision of Prof. M. de Jong, EMC, Rotterdam) the DOTA-DGlu-DGlu-DGlu-DGlu-DGlu-DGlu-Ala-Tyr-Gly-Trp-Met-Asp-Phe-NH2 (CP04) showed the most promising characteristics in terms of high stability and receptor affinity, high and persistent tumour uptake and low kidney retention and was therefore selected for this clinical evaluation.

The aim of the project is to establish in a multinational cooperation in the innovative field of targeted radionuclide therapy using the CCK-2/gastrin receptor-seeking ligand CP04 radiolabelled with Indium-111 (111In) as imaging biomarker.

Study objective

Primary Objectives
1. to establish the safety of intravenous administration of a therapeutic peptideamount of the CP04
2. to assess the biodistribution and dosimetry of 111In-CP04 in cancer and normal tissues and to determine critical organs.
Secondary Objectives
1. to evaluate the diagnostic potential of CCK2/gastrin receptor ligand-scintigraphy to detect cancer lesions for both diagnostic and therapeutic peptide amount
2. to evaluate the influence of a diagnostic amount of CP04 peptide on the therapeutic amount of peptide vs. a therapeutic amount of peptide alone on tumour and organ uptake
3. to investigate the relative decrease of kidney dose after co-administration of nephroprotective agent * Gelofusine

Study design

The study is a phase I multicentre randomized, open, parallel-arm clinical trial

Intervention

The research will undergo a scan with IN111-CP04 and possibly an administration of Gelofusine if by lottery assigned

Study burden and risks

It is expected that within the outcomes of this project, the CCK-2/gastrin receptors become viable targets for radionuclide scintigraphy and radionuclide therapy, similarly to somatostatin receptors which were instrumental to establish nuclear medicine efficacy in clinical practice. The novel vector may get a chance to be introduced to clinical practice as a more selective and efficient tool for the diagnosis, early detection and therapy of recurrent and metastatic MTC. Furthermore, the results of this project may become the first step to establish a new, more effective strategy for the treatment of MTC patients, leading to reduction mortality as well as improvement of quality of life of these patients.
Treatment options for MTC patients are very limited. According to data that have been generated by different clinical research groups, treatment with

labelled CP04 may offer a safe and promising approach for MTC patients that would until now receive sole best supportive care.
Side effects to be expected are limited and comparable with side effects of a Pentagstrin® stimulation test or side effects seen after administration of Demogastin 2, a recently investigated CCK-2R binding analogue. These are self-limiting complaints like dizziness, flush, rise in heart rate, pressure on the chest, nausea, and rarely some hypotension. These side effects disappeared spontaneously, mostly within some minutes. Other potential risks are haematomaof infection caused by intravenous drips or blood samples. Radiation dose caused by administration of 111In-CP04 is within current levels of standard diagnostic procedures. Depending on the medical situation of the patients included in the study, they might have benefit for their own treatment. Overall, the investigators believe that the benefits outweigh the risks for the individual patient.

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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. Histologically documented medullary cancer of the thyroid.
2. Presence of more than one distant or nodal, surgically untreatable metastases confirmed with either 18F-FDG PET/CT or enhanced-CT or MRI.
3. Doubling time (DT) of serum calcitonin level within two years prior to study entry and no evidence of disease.
4. Karnofsky performance status >50%.
5. Life expectancy of more than 6 months.
6. Male or female patients aged >18 years without upper age limit.

Exclusion criteria

Related to the MTC:
1. Patients with surgically treatable medullary thyroid cancer.
2. Patients with history of second malignancy other than basal cell carcinoma of the skin.
Related to previous or concomitant therapies :
3. Participation in any other investigational trial within 3 months of study entry.
4. Previous external beam radiation therapy within two years.
5. Organ allograft requiring immunosuppressive therapy.
6. Treatment with Tyrosine kinase inhibitors
Related to the patient:
7. Pregnancy, breast-feeding.
8. Known hypersensitivity to gastrin analogues.
9. Patients with concurrent illnesses that might preclude study completion or interfere with study results.
10. Patients with bladder outflow obstruction or unmanageable urinary incontinence.
11. Clinical diagnosis of disseminated intravascular coagulation.
12. Serum creatinine >170 *mol/L, GFR < 40 mL/min
13. Known history of hypersensitivity to Gelofusine or any other contraindications to Gelofusine infusion

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-02-2018
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gelofusine
Generic name:	Succinylated Gelatin
Product type:	Medicine
Brand name:	nvt
Generic name:	111-In-CP04
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	25-04-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-11-2017
Application type:	First submission

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2015-000805-38-NL
CCMO	NL55280.078.16
Other	UR.DBL.BLE.475.0324.2015