Improving Treatment Options for Somatostatin Type 2 Receptor Negative Neuroendocrine Tumor Patients

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The aim of this prospective proof-of-concept study is to increase the expression of the SSTR2 in NET patients with negative or low expression to levels amenable for somatostatin analogue treatment through the use of epigenetic drugs.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neoplastic and ectopic endocrinopathies
Study type	Interventional

Summary

ID

NL-OMON55794

Source
ToetsingOnline

Brief title
IMPROVE-NET trial

Condition

- Neoplastic and ectopic endocrinopathies
- Endocrine neoplasms malignant and unspecified

Synonym
carcinoid, neuroendocrine tumor

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Erasmus MC Vriendenfonds

Intervention

Keyword: epigenetic drugs, Gallium-DOTATATE PET-CT, neuroendocrine tumor, somatostatin receptor

Outcome measures

Primary outcome

The primary endpoint will be the percentage of patients that after treatment

will have an uptake of 68Ga-DOTATATE that is at least one point higher on the

Krenning scale.

Secondary outcome

Secondary endpoints include safety monitoring, circulating drug levels,

dosimetric evaluations and leucocyte methylation analysis.

Study description

Background summary

Somatostatin receptor type 2 (SSTR2) expressions are of eminent importance for the staging and treatment of neuroendocrine tumors (NETs). The clinical benefit obtained by treatment with unlabeled and radiolabeled somatostatin analogues does not apply to the subset of patients with SSTR2-negative or low expression tumors. The lack of these anti-tumoral options could be responsible for the inferior outcome of these patients compared to those with SSTR2-positive tumors. Recent in vitro data showed the possibility of upregulating SSTR2 expression in pancreatic NET cells through treatment with epigenetic drugs. Translating these methods into clinic could substantially improve diagnostic and treatment options for patient with SSTR2-negative or low expression tumors.

Study objective

The aim of this prospective proof-of-concept study is to increase the expression of the SSTR2 in NET patients with negative or low expression to levels amenable for somatostatin analogue treatment through the use of epigenetic drugs.

Study design

Interventional proof-of-concept self-controlled study

Intervention

14 days treatment with valproic acid (30mg/kg body weight/day)

Study burden and risks

We consider the risk of this study to be minor, as both valproic acid is a well known drug and treatment duration is limited to 14 days. The most commonly reported toxicity of the study drugs were distal tremor, nausea and drowsiness. As a safety precaution, patients with impaired kidney function (creatinine clearance <50ml/min) and liver disease (liver transaminases >3 times upper normal range) will be excluded. In case of patients reporting toxicity, individual evaluation concerning dosage reduction or additional treatment will be undertaken.
After inclusion, blood samples will be drawn at baseline and at the two consecutive visits (day 7 & day 14), total additional amount of blood taken will be 3x 20ml.
At day 14, an additional 68Ga-DOTATATE-PET scan will be performed. The radiation dosage for the additional 68Ga-DOTATATE-PET CT scan is around 5.8 mSv. Given the possible gain of over 5 years progression free survival the risk-benefit ratio for this study is deemed positive.

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

• Age >=18 years
• Inoperable or metastasized neuroendocrine tumor with well-differentiated histology (grade 1, 2 or 3)
• SSTR2 negativity or low uptake on 68Ga DOTATATE PET scan, defined as tumor uptake on 68Ga-DOTATATE PET CT below that or equal to that (Krenning Score 1 or 2) of the liver

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Hypotension, defined as systolic blood pressure <90mmHg
• Heart failure, defined as NYHA III-IV
• Impaired kidney function, defined as creatinine clearance <50ml/min
• Impaired liver function, defined as bilirubin or liver transaminases >3 times upper normal range
• Epilepsy
• Known allergies / intolerances to valproic acid or hydralazine
• Existing drug treatment which cannot be stopped and interacts or interferes with study drugs
• Inability to provide informed consent
• End of life care

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-07-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gallium68-DOTA-0-Tyr3-Octreotate
Generic name:	Gallium68-DOTA-0-Tyr3-Octreotate
Product type:	Medicine
Brand name:	Valproic acid
Generic name:	Valproic acid
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	28-03-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	19-04-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO

Date:	03-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2021
Application type:	Amendment
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	EUCTR2018-004091-35-NL
CCMO	NL67891.078.18
Other	NL7726