Investigating the occurrence of everolimus long-term side effects by follow up of everolimus trough blood concentrations.

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Primary Objective: To investigate the association between the everolimus trough levels over time and the onset of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 grade 2, 3 or 4 late AEs (i.e. from treatment...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON50487

Source
ToetsingOnline

Brief title
Everolimus TDM to predict long-term toxicity

Condition

- Other condition
- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, renal cell carcinoma and neuroendocrine tumours

Health condition

mRCC en (p)NET

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Dried Blood Spot (DBS) method, Everolimus, Long-term side effects, Therapeutic Drug Monitoring (TDM)

Outcome measures

Primary outcome

The difference in percentage of patients with a high everolimus trough level

(i.e. > 18 ng/mL) experiencing NCI-CTCAE v4.0 grade 2, 3 or 4 late AEs (i.e.

toxicity reported from >= 12 weeks onward, e.g. pneumonitis, anorexia, anemia)

compared to participants with lower trough concentrations.

Secondary outcome

1. The difference in percentage of patients with a high everolimus trough level

(i.e. > 18 ng/mL) experiencing NCI-CTCAE v4.0 grade 2, 3 or 4 late AEs (i.e.

from treatment period < 12 weeks, e.g. stomatitis) compared to participants

with lower trough concentrations.

2. To define the correlation between everolimus concentration measured in whole

blood after a venipuncture as compared to the everolimus concentration measured

from dried capillary blood extracted from the Whatman filterpaper of the DBS.

3. To define the correlation between everolimus concentration collected with

DBS from a finger prick and DBS paper spiked with a drop of everolimus from venipunctured whole blood from the Whatman filterpaper of the DBS.

4. To define the correlation between the everolimus trough levels (over time) between patients using full dose everolimus (e.g. 10 mg once daily) and patients using everolimus in a reduced dose (e.g. 2,5 or 5 mg once daily) at each moment of blood sampling in time.

Study description

Background summary

Metastatic (Hormone-Receptor [HR]-positive, HER2-negative) breast cancer (BC), advanced or unresectable neuroendocrine tumours of pancreatic (pNET), gastrointestinal or lung origin and metastatic renal cell carcinoma (mRCC) are diseases with poor outcome. Everolimus is part of palliative treatment and increases patients* median progression-free survival (PFS) with 4.6 months in metastatic BC (mBC), 7 months in (p)NET and 3 months in mRCC. However, serious adverse events (AEs) occur frequently; stomatitis up to 67%, pneumonitis up to 15%. This reduces effectiveness of everolimus, because AEs are managed with dose reductions, treatment interruptions or even complete discontinuation of everolimus.

Therapeutic-drug-monitoring (TDM) (i.e. measurement of everolimus whole blood levels after venipuncture) is used to adjust the prescribed daily dose, to maintain effective everolimus whole blood concentrations, with the lowest possible risk of AEs. In addition, TDM is a useful tool for early detection of non-adherence, and might also be used to monitor the effects of drug-drug interactions and food effects.While TDM has been common in transplantation medicine for 10 years, it has not been implemented in oncology. The importance of TDM in oncology is, however, supported by previous research which showed that a 2-fold increased everolimus whole blood trough concentration (Cmin) was associated with a short-term risk of grade >= 3 pulmonary events (relative risk [RR] 1.9; 95% CI 1.1-3.3], stomatitis events (RR 1.5; 95% CI 1.1-2.1) and metabolic events (RR 1.3 95% 1.0-1.7). Moreover, an exposure-toxicity relationship of everolimus in patients with thyroid cancer was observed, since initial everolimus concentrations could be associated with early toxicity (< 12 weeks), i.e. stomatitis. However, the association between initial everolimus

measurements) and long-term AEs (>=12 weeks, e.g. pneumonitis, anorexia and anemia) of any grade and the need for everolimus dose reductions could not be made. Since levels ±>18 µg/L were associated with toxicity, we assume that the upper therapeutic window of everolimus in the oncologic setting will be ±18 µg/L. Therefore, an upper threshold of >18 µg/L was considered for this study. Similarly, a tendency to improved PFS and overall survival (OS) was observed when Cmin in steady state (CminSS) was above 14.1 µg/L. This seems to be the lower limit of the therapeutic window.

However, the following knowledge gaps exist: 1. It is unknown whether everolimus whole blood trough levels (over time) predict long-term AEs (e.g. pneumonitis, anorexia and anemia). 2. The optimal concentration range for everolimus, with the treatment of mBC, mRCC, or (p)NET is unknown, especially the upper limit associated with toxicity. 3. It is unknown what everolimus concentration level is associated with the need for everolimus dose reductions.

Study objective

Primary Objective:
To investigate the association between the everolimus trough levels over time and the onset of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0 grade 2, 3 or 4 late AEs (i.e. from treatment period >=12 weeks onward).

Secondary Objective:
- To investigate the association between the everolimus trough levels over time and the onset of NCI-CTCAE v4.0 grade 2, 3 or 4 early AEs (i.e. from treatment period < 12 weeks).
- To establish the association of trough concentrations of everolimus obtained via venipuncture and trough concentrations obtained via finger prick in the oncology population.
- To assess the feasibility of the novel finger prick DBS method in the oncology setting.
- To investigate the association between everolimus trough levels (over time) and the need for everolimus dose reductions.

Study design

Observational cohort study

Study burden and risks

The research is low-risk as there are minimal invasive procedures. Subjects can experience pain, irritation and redness of the skin after the collection of blood via the venous blood method and the finger prick method (NB. the finger prick method will only be performed for patients treated in the MUMC+ or

Radboudumc hospital). Furthermore, patients need to keep up with their diary.
The use of everolimus is associated with adverse effects, however, these adverse effects are not related to this study.
There will be no direct benefit to the participants.
The importance of the study is to investigate the association between the bloodconcentration and the long term adverse effects of everolimus.

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

-Patients currently treated with everolimus for any type of cancer, such as the EMA registered indications i.e. advanced (Hormone-Receptor [HR]-positive, HER2-negative) breast cancer, metastatic renal cell carcinoma (mRCC) or neuroendocrine tumour (NET) of pancreatic, gastrointestinal or lung origin.

-Aged 18 or above
-Able and willing to sign the informed consent

Exclusion criteria

-No informed consent
-Alactasia
-Lenvatinib combination therapy with everolimus (mRCC)

Study design

Design

Study phase:	4
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-09-2017
Enrollment:	40
Type:	Actual

Ethics review

Approved WMO Date:	01-05-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	23-10-2017

Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	07-02-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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	NL58486.068.17
Other	not yet assigned: clinicaltrials.gov