prediction of everolimus-induced interstitial lung disease in breast cancer patients; maximizing efficacy by reducing toxicity

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Primary objective:Analyze the value of pneumoproteins, everolimus exposure, pulmonary function tests, distinct radiological patterns, baseline patient characteristics and the development of skin toxicity or oral mucositis for the prediction of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Observational invasive

Summary

ID

NL-OMON38563

Source
ToetsingOnline

Brief title
PREVENT

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mamma carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud

Source(s) of monetary or material Support: subsidie bij pink ribbon en Novartis is aangevraagd

Intervention

Keyword: adverse events, everolimus, personalized care, prediction

Outcome measures

Primary outcome

Find the correlation between:

- baseline patient characteristics (smoking, preexistent lung disease)

- pneumoproteins; KL-6, surfactant protein A, surfactant protein D, CC16,

CCL18, YKL-40, LDH and CA 15.3 (absolute number and difference from baseline)

- everolimus exposure (AUC on day 14 and mini-AUC at moment of toxicity)

- pulmonary function tests: spirometry including FVC and DLCO adjusted for

hemoglobin (absolute number and difference from baseline)

- four distinct radiological patterns of 1.0mm CT slices of the lungs (as

described in paragraph 6.2.7, page 30)

- the development and grade of everolimus-induced skin toxicity and oral

mucositis

and the development and grade of everolimus-induced ILD, using univariate and

multivariate analysis.

Secondary outcome

- Analyze the temporal relationship between a decrease in pulmonary function or

the occurrence of new radiological pulmonary abnormalities and an increase in

the level of pneumoproteins

- Investigate which immunological changes (cytokines, T-cells, dendritic cells)

are observed in peripheral blood, skin biopsies and bronchoalveolar lavage of patients with everolimus-induced toxicity

- Assess the duration and severity of ILD when patients are treated according to a standardized diagnostic and treatment strategy

- Define the correlation between everolimus induced ILD on the one hand and everolimus exposure (as per AUC0-24h) on day 14) and outcome (as per PFS) on the other hand

- Determine the type and frequency of lung parenchymal changes and its discriminative power from other (not drug-related) lung changes

- Describe the quantity and quality of differences in judgment of HRCT images between a local and a central radiologist

- Correlate everolimus exposure in saliva with serum AUC

- Correlate everolimus exposure in saliva with incidence of oral mucositis

Study description

Background summary

In postmenopausal women with advanced hormone receptor-positive breast cancer, treatment with everolimus in combination with exemestane can restore the sensitivity of the tumor to hormone therapy, and thereby offers an effective alternative to a chemotherapy regime. The use of everolimus, however, can be complicated by adverse events such as interstitial lung disease (ILD), i.e., pneumonitis. Due to an increased awareness of ILD and inclusion of radiological findings using high resolution (HR) CT, nowadays ILD is reported in 10-40% of patients. However, only retrospective studies have been performed. Most patients are asymptomatic or mildly symptomatic, but in some patients ILD will cause serious pulmonary problems. Therefore, it is important to enable discrimination between patients in whom everolimus can be continued safely and in whom discontinuation is indicated. At this moment no data are available to aid in this distinction. Early and non-invasive markers that can predict the development and severity of everolimus-induced ILD would therefore be of great

clinical value.
Additionally, the pathophysiology of everolimus-induced ILD is unclear. Furthermore, there is no standardized strategy for everolimus induced ILD. A more thorough understanding of this pathophysiology can aid in the development of rational and more effective management strategies of this hazardous side effect.
To resolve these clinically relevant problems prospective data investigating everolimus-induced ILD are needed, especially in the vulnerable metastatic breast cancer patient.

Study objective

Primary objective:
Analyze the value of pneumoproteins, everolimus exposure, pulmonary function tests, distinct radiological patterns, baseline patient characteristics and the development of skin toxicity or oral mucositis for the prediction of the development and severity of everolimus-induced ILD.

Secondary objectives:
- Determine whether a decline in pulmonary function test or the occurrence of new radiological pulmonary abnormalities is preceded by an increase in the level of pneumoproteins
- Investigate the pathophysiology of everolimus-induced ILD, skin toxicity and oral mucositis
- Describe the outcomes of a standardized treatment strategy for everolimus-induced ILD
- Correlate the development and grade of everolimus-induced ILD, skin toxicity and oral mucositis with everolimus exposure (AUC) and outcome (PFS)
- Determine the type and frequency of lung parenchymal changes and its discriminative power from other (not drug-related) lung changes
- Determine the impact of radiological interreader variability on patient management (e.g., expert opinion versus general radiologist)

Study design

This is a prospective post registration, multicenter study. After starting treatment with everolimus and exemestane patients will be monitored during six months for the development of pulmonary complications as well as skin toxicity and oral mucositis. Hereafter patients will be followed until treatment with everolimus and exemestane is discontinued. The moment and reason for everolimus and exemestane discontinuation will be recorded.

Study burden and risks

The study procedures will be performed at the moments that patients will visit their clinic for standard patient care, so no extra visits are needed.

Patients will be asked to keep a diary in which they will record their adverse events. Extra blood (80 ml per visit) will be drawn on moments where blood is drawn in standard patient care, therefore no extra venous punctures will be necessary. Patients will undergo PFT six times for study purposes, which will take about 15 minutes per PFT. Tumor response with a chest CT will be evaluated after three and six months of treatment, so no extra CT-scans will be necessary. From this chest CT 1.0mm CT slices of the lungs will be obtained. No extra radiation dose or intravenous contrast injection will be necessary. On day 14 patients have to visit their clinic for PK analysis, where a total of six blood samples will be taken via an intravenous cannula, up to 8 hours after everolimus ingestion. In addition, a trough level everolimus will be measured in saliva.

If ILD or grade * 2 skin toxicity or oral mucositis develops, extra blood (74 ml) will be drawn, PFT will be repeated and a 2-3mm skin biopsy will be performed if patients agree.

Benefits associated with participating in this study are that patients and their treating physician will be extra alert on the development of adverse events, especially ILD. The treating physician is provided with a detailed management strategy, which aids in treating this toxicity optimally.
In addition, everolimus exposure will be measured. If the treating physician thinks it is in the best interest of the patient he/she can obtain the results from the principal investigator and is free to change the dose according to his/her own judgment.

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

Eligible for inclusion are women who are planned to start treatment with everolimus in combination with exemestane as decided by their treating physician, if the patient is willing and able to sign the Informed Consent Form. The following general criteria can be used to determine whether a patient is suitable for treatment with everolimus and exemestane. Renal insufficiency and pulmonary disease are not considered an exclusion criterion.
- Adult women with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.
- Histological or cytological confirmation of estrogen-receptor positive (ER+) breast cancer
- Postmenopausal women. Postmenopausal status is defined either by:
o Age * 55 years and one year or more of amenorrhea
o Age < 55 years and one year or more of amenorrhea, with an estradiol assay < 20 pg/ml
o Surgical menopause with bilateral oophorectomy
- Radiological or clinical evidence of recurrence or progression on last systemic therapy prior to enrollment
- Resistance to treatment with a non-steroidal aromatase inhibitor
- Serum platelets * 100x10E9/l
- Everolimus dose adjustment is recommended for patients with hepatic impairment (Child-Pugh A/B/C)
- Performance status ECOG 0 - 2 (Karnofsky index: 60 - 100)

Exclusion criteria

- Patients with a HER2-overexpressing tumor by local laboratory testing (IHC 3+ staining or amplification defined as locus/centromere ratio > 2.2 on fluorescent situ hybridization (FISH) or cytochromic in situ hybridization (CISH))
- Known hypersensitivity to mTOR inhibitors, e.g. sirolimus (rapamycin).
- Patients with a known history of HIV seropositivity or hepatitis B or C

- Uncontrolled diabetes mellitus
- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)
- Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-04-2014
Enrollment:	100
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	Everolimus
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	14-08-2013
Application type:	First submission

Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-08-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-03-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-12-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2013-002258-60-NL
CCMO	NL45027.091.13