The effect of bevacizumab on taxanes-mediated release of growth factors and bone marrow derived endothelial progenitor cells.

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This study has two primary objectives:To determine the effect of taxane therapy on the release of bone marrow derived endothelial progenitor cells.To study the effect of bevacizumab on taxane induced release of bone marrow derived endothelial...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON31128

Source
ToetsingOnline

Brief title
endothelial cell-platelet study

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, malignancy

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Roche

Intervention

Keyword: bevacizumab, endothelial progenitor cells, platelets, taxanes

Outcome measures

Primary outcome

To clarify the mechanism of the occurrence of the endothelial progenitor cell burst that occurs after chemotherapy by :

Determining the effect of taxane therapy on the release of bone marrow derived progenitor endothelial cells.

Studying the effect of bevacizumab on taxane induced release of bone marrow derived progenitor endothelial cells

Secondary outcome

To explore whether there is a difference in progenitor cell dynamics between paclitaxel and docetaxel and a weekly or threeweekly regimen.

To determine whether anti-angiogenic treatment affect platelet biology by testing:

1) Whether anti-angiogenic treatment impairs the angiogenic activity of isolated platelets from patients receiving bevacizumab treatment by using an endothelial cell proliferation assay as a potential biomarker for bevacizumab activity.

2) Whether platelets markers of activation can be detected in platelet samples or plasma from patients receiving bevacizumab treatment.

3) Whether platelet function is changed in aggregation and activation studies

in vitro of isolated platelets from patients receiving bevacizumab treatment.

Study description

Background summary

Recent findings have demonstrated that taxanes (and perhaps several other chemotherapeutics) induce an immediate release of bone marrow progenitor endothelial cells. This release occurs within hours after administering chemotherapy to the patient. The clinical relevance of the release of bone marrow derived cells is currently unclear. In preclinical tumor models perturbation of the tumor with a vascular disrupting agent induces a similar release which coincides with rapid re-growth of the tumor. In addition, preliminary preclinical experiments suggest that bevacizumab may prevent the release of bone marrow derived endothelial cells. We have also found that platelets take up bevacizumab which subsequently neutralizes VEGF stored in the alpha granules. Blockade of platelet VEGF may reduce their normal angiogenic potential. Reduction of their angiogenic potential can be measured in endothelial cell proliferation assays and may be used as a potential biomarker for bevacizumab activity. Since platelets are important in wound healing and coagulation, impaired platelet function may also have adverse effects in patients treated with bevacizumab. For example, bowel perforations may be explained by this mechanism. There are no studies specifically addressing this question.

Study objective

This study has two primary objectives:
To determine the effect of taxane therapy on the release of bone marrow derived endothelial progenitor cells.
To study the effect of bevacizumab on taxane induced release of bone marrow derived endothelial progenitor cells

Secondary objectives are:
To determine the type of taxane and schedule on the release of bone marrow derived endothelial cells.
To determine the effect of bevacizumab monotherapy and in combination with taxane chemotherapy on platelet biology and angiogenic growth factors

Study design

A translational study in which primary endpoint is concerning biomarker dynamics and not efficacy or safety of the drugs being administrated.
This study is designed as a two step translational study in which we study in part A in the first 2 cohorts of 12 patients whether docetaxel and paclitaxel in most frequently used clinical dosing regimens induce a release of progenitor cells from the bone marrow in the circulation and whether this release can be inhibited by bevacizumab. After these two cohorts we will proceed with the second part B of the study with two different dosing schedules of Docetaxel and Paclitaxel if indeed a release of progenitor cells upon treatment with either Docetaxel or Paclitaxel occurred.

Intervention

Patients will be randomly assigned to cohorts, with or without a predose consisting of bevacizumab.
Other interventions include venapunctures for bloodsampling.

Study burden and risks

Extent of burden for the participating patients consitst mainly of the time that they have to spent extra in the hospital, and the times they have to come back to the hospital. Also the extra bloodsampling by a second iv catheter might be a burden.
The administration of bevacizumab can cause side effects which can also be a burden.
The benefit for the patients is the addition of bevacizumab to the regular treatment.

Contacts

Public
Academisch Medisch Centrum

Heidelberglaan 100
3584 CX Utrecht
Nederland
Scientific
Academisch Medisch Centrum

Heidelberglaan 100
3584 CX Utrecht
Nederland

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

The patient will have a previous diagnosis of histologically or cytologically documented solid tumor.
The patient will start a taxane containing regimen as first or second line chemotherapy according to standard treatment guidelines for the underlying disease. Patients with metastatic or locally advanced breast cancer will be eligible.
The patient has given written informed consent.
The patient is willing and able to comply with protocol procedures.
The patient must be *18 years of age.
The patient will have not received any chemotherapy or biological therapy within the last 28 days and has recovered from any acute effects.
Performance status WHO 0-2

Exclusion criteria

Surgery < 3 weeks prior to the start of study treatment
Inadequate recovery from previous surgery, radiation, chemo-, biologic or immunotherapy
Patients who have known hypersensitivity to the study medication, ie bevacizumab and taxane containing chemotherapy
concurrent severe and/or uncontrolled medical conditions which could compromise participation in the study (details in protocol)
Laboratory evaluation disturbances (details in protocol)
Previous neuropathy grade II
Squamous cell tumors adjacent to the large thoracic vasculature

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2007
Enrollment:	48
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxotere
Generic name:	Docetaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-09-2007
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-03-2008
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	18-02-2009
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2007-004119-79-NL
CCMO	NL18958.041.07