Evaluation of VEGF expression with 89Zr-bevacizumab PET scan in patients with relapsing multiple myeloma; a feasibility study.

Published: 10-07-2012
Last updated: 26-04-2024

In the present study we will perform a feasibility study to demonstrate that 89Zirconium-bevacizumab PET scanning can visualize multiple myeloma lesions. Data from the present study may be used to design further studies with regard to the expression…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Plasma cell neoplasms
Study type	Observational invasive

Summary

ID

NL-OMON37271

Source
ToetsingOnline

Brief title
89Zr-bevacizumab PET MM

Condition

- Plasma cell neoplasms
- Bone disorders (excl congenital and fractures)

Synonym
Multiple myeloma AND Kahler's disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: 89Zr-bevacizumab PET, Angiogenesis, FDG-PET, Multiple myeloma

Outcome measures

Primary outcome

The primary endpoint will be 89Zr-bevacizumab tracer uptake in multiple myeloma lesions

Secondary outcome

The secondary endpoints will be:

• The correlation between positive lesions found on the FDG-PET and lesions found on 89Zr-bevacizumab PET scan.

• The correlation between VEGF levels and MVD in bone marrow samples of MM patients and lesions found on 89Zr-bevacizumab PET scan.

Study description

Background summary

Multiple Myeloma (MM) is a clonal B cell disorder characterised by a monoclonal plasma cell population in bone marrow, with bone pain, anaemia, hypercalcaemia, and kidney dysfunction as clinically presenting symptoms. Osseous involvement is one of the most predominant features of patients with MM; 90% of the patients develop lytic bone lesions. Lytic bone lesions are the result of increased bone resorption and reduced bone formation. The regular method to detect bone lesions is skeletal survey. This technique can only detect lesions that have lost 30% or more of the trabecular bone. Another weakness is the fact that lesions persist after treatment with chemotherapy or radiotherapy and no clear distinction can be made whether vital tumour cells persist in these lesions. New bone lesions are a sign of disease progression. Furthermore they

give clinical signs as bone pain and in the worse case scenario pathological fractures. Alternative scanning methods have been developed to visualize the malignant plasma for example by making use of enhanced metabolic activity of the plasma cells defined by the uptake of 18F-fluorodeoxyglucose -Positron Emission tomography (FDG-PET. The use of FDG-PET in newly diagnosed MM patients is well studied.

The increased FDG-uptake by the tumour is related to a high metabolic activity. This might be a consequence of tumour hypoxia causing new vessel formation. There seems to be a relationship between MM and angiogenesis, the formation of new blood vessels from exciting blood vessels. There is an increased microvessel density (MVD) of the affected bone marrow in patients with active MM. Vascular endothelial growth factor (VEGF) is an important mediator of angiogenesis. MM cell lines were found to express VEGF mRNA and secrete the protein in the extracellular environment thereby stimulating angiogenesis.

Inhibition of the process of angiogenesis is used in the treatment of MM, for instance by means of thalidomide and lenalidomide. Blocking VEGF itself can be obtained by means of bevacizumab, a recombinant, humanised monoclonal antibody that binds to all isoforms of human VEGF with high affinity. Treatment with bevacizumab is well established in solid tumours, like colon cancers and renal cell carcinomas and is currently tested in acute myeloid leukaemia and MM.

VEGF imaging with radiolabeled bevacizumab has been developed. Bevacizumab binds VEGF and can be labeled with the PET isotope Zirconium-89 (89Zr) while preserving VEGF binding properties. In a human ovarian tumor xenograft, PET imaging 24 hours after injection of 89Zr-bevacizumab showed high uptake in well perfused organs and in the tumor. A feasibility study in our institution, with 89Zr-bevacizumab PET imaging in renal cell carcinoma patients, showed a superior diagnostic yield compared to other imaging techniques.

The high VEGF production by myeloma cells makes VEGF a very interesting target for tumor visualization. 89Zr-bevacizumab PET imaging could be more sensitive for myeloma lesions.

So, in conclusion, VEGF is expressed by MM plasma cells, thereby providing a rationale that the assessment of VEGF-levels in the micro-environment of MM tumors could potentially be used as a diagnostic tool to see if there is disease activity. Especially in the relapsed setting this is of invaluable importance, since conventional skeletal survey has limitations in this setting. Furthermore, 89Zr-bevacizumab PET imaging could provide information about treatment options and treatment response.

Study objective

In the present study we will perform a feasibility study to demonstrate that 89Zirconium-bevacizumab PET scanning can visualize multiple myeloma lesions.

Data from the present study may be used to design further studies with regard to the expression of VEGF and the selection of patients for anti-angiogenic therapy. It might predict which patient will benefit from anti-angiogenetic treatment and for future studies to see which patient might benefit from adding bevacizumab to the treatment regime. Furthermore, 89Zirconium-bevacizumab PET scanning can be used for monitoring therapy effect and the degree of uptake defined by SUV might also provide prognostic information.
In addition, in vitro staining of bone marrow material will be performed to demonstrate whether VEGF is up regulated by the malignant plasma cells or surrounding cells. Furthermore, the MVD will be defined. These results will be combined with the results of the 89Zr-bevacizumab PET imaging to see if there is a correlation between positivity of the 89Zr-bevacizumab PET imaging and up regulation of angiogenesis parameters.

Study design

This is a pilot-study, thus no formal group size calculation can be given. For the purpose of this study, 20 patients will be included. Patients must have a relapsing multiple myeloma according to international guidelines. A bone marrow biopsy and a FDG-PET scan will be performed. It is expected that 20 patients will cover the variability of the 89Zr-bevacizumab uptake of MM patients. Currently, the total number of patients fulfilling the eligibility criteria of this study is 20-30 on a yearly basis.

4.1 Timetable baseline T=0 T=1

Evaluation
in-exclusion criteria X
Informed consent X
FDG-PET scan X
Bone marrow biopsy X
89Zr bevacizumab injection X
89Zr bevacizumab imaging X

T=1: 4 days aftertracer injection

Study burden and risks

Adverse event that are related to 89Zr-bevacizumab PET imaging:
- Hypersensitivity reactions to bevacizumab within a short term after administration (within 3 hours).
- Hypertension can occur after administration of bevacizumab. However the risk is considered minimal due to the low tracer dose used in this study (see IMPD).
So far no side effects have been seen using 89Zr-bevacizumab

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 with relapsing multiple myeloma according to international defined guidelines:;Relapse after having achieved complete remission:
1. Reappearance of paraprotein
2. More than 5% plasma cells in bone marrow.
3. New lytic lesions or progression of old lesions.
4. New hypercalceamia.;Relapse after having achieved partial remsission
1. Increases of paraprotein with more than 25%
2. Increase of urine paraprotein with more than 25%
3. Increase of plasma cells in bone marrow with 10%
4. New lytic lesions or progression of old lesions
5. New hypercalceamia

Exclusion criteria

- Radiotherapy in the last 3 months.
- Ineligible to lay supine during the PET scan.
- Age <=18 years.
- Pregnancy.
- Claustrophobia
- Severe kidney dysfunction; serum-creatinine >=250 µM

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-09-2013
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Avastin
Generic name:	Bevacizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	10-07-2012

Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-01-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-002335-28-NL
CCMO	NL40614.042.12