Effects of bortezomib on bone turnover during treatment of relapsed multiple myeloma: a pilot study of quantitative in-vivo monitoring.

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

Summary

ID

NL-OMON32496

Source
ToetsingOnline

Brief title
Bone turnover in multiple myeloma.

Condition

- Plasma cell neoplasms

Synonym
multipel myeloma, plasma cell disease

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W,industrie,Janssen-Cilag

Intervention

Keyword: bone turnover, bortezomib, multiple myeloma

Outcome measures

Primary outcome

Primary endpoint

- Accurateness of the [18F]PET/CT scans to depict bone turnover in vivo and on site

- Bone turnover before and after completion of bortezomib treatment.

Secondary outcome

Secondary endpoints

- Bone turnover in patients with a documented anti-MM response on bortezomib versus patients without a response on bortezomib (according to the response criteria in appendix C). Separate analysis for the qualitiy of response will be performed.

Study description

Background summary

The persistence of suppressed bone formation in multiple myeloma patients even after a good response to therapy is of concern in view of the morbidity of the persisting risk of skeletal events. The availability of an agent that restores bone formation at pathological sites would be a major innovation in MM therapy, even in a palliative setting. The proteasome inhibitor bortezomib (Velcade®) has a positive effect on bone formation reflected by biochemical markers in serum and by an increase in activated osteoblasts in bone marrow biopsies. Still, it remains to be demonstrated that bortezomib (Velcade®) actually leads to an on-site restoration of bone formation at pathological sites, eventually resulting in a decline in skeletal related events.

This study aims at visualizing the process of disease activity and bone formation at pathological sites in correlation with in vitro markers of bone turnover. The only known method to measure bone turnover is invasive:by bone biopsies. Fluoride-PET scan can quantitatively measure bone turnover, at the site of the osteolytic lesion and is non-invasive and thus could be used more easily and frequently in patients. The pilot study is for validating the accurateness of this quantitative in-vivo on-site imaging technique. The main hypothesis is that treatment with bortezomib (Velcade®) results in normalized or enhanced bone formation especially in areas of osteolysis. The second goal of the study is to determine whether restoration of bone turnover is coupled to the response of anti-myeloma therapy.

Study objective

1. The accurateness of the imaging techniques will be evaluated for quantitatively measuring in-vivo and on-site bone turnover in this specific category of patients, i.e. patients with myeloma bone disease.
Bone turnover will be measured using
* in vivo imaging techniques to actually monitor on-site effects in terms of bone remodelling and disease activity.
* in vivo determination of bone osteoblast number and bone mineral apposition rate (MAR).
* in vitro markers reflecting osteoclast activity, bone degradation, osteoblast activity and bone formation.
2. To determine if bortezomib restores bone remodelling in MM patients with active bone disease at pathological sites.
Bone turn over will be measured using
* in vivo imaging techniques to actually monitor on-site effects in terms of bone remodelling and disease activity,
* in vitro markers reflecting osteoclast activity, bone degradation, osteoblast activity and bone formation.
3. To determine if bortezomib-induced changes in bone-remodeling are related to anti-MM activity, or are exerted independently of disease response

Study design

The design of the study is a prospective non-randomised single center cohort study of patients with relapsed myeloma referred for treatment with bortezomib. Patients are required to have at least one osteolytic lesion. Bone turnover and disease activity will be assessed after inclusion and after completion or discontinuation of treatment.
The number of patients to be included must be large enough to demonstrate proof of principle. Depending on the treatment status of patients before inclusion, an expected (partial response or better) response rate of 30-50% after completion of 8 cycles of bortezomib is to be expected. Bone turnover will be measured both in responding and non-responding myeloma. In order to have at

least 10 patients in both of these groups, the aim is to include 25 consecutive patients.
After inclusion of the first five patients completing at least 4 cycles of bortezomib, an interim analysis of the imaging techniques will be performed. If satisfactory discrimination of changes in bone turnover can be visualized in these five patients (see paragraph 17.1), the study will be continued.

Study burden and risks

see point E

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

Inclusion criteria
* Patients with relapsed or progressive multiple myeloma who did not receive treatment with bortezomib before, and requiring treatment
* At least one manifest osteolytic lesion
* Age 18-75
* Not on active treatment with dexamethasone in the last 4 weeks, or requiring immediate treatment with dexamethasone
* Patients on bisphosphonate treatment are allowed if bisphosphonates were started * 3 months before registration
* WHO performance 0-2 (Appendix A)

Exclusion criteria

* Polyneuropathy * grade 2
* Severe cardiac dysfunction (NYHA classification II-IV, appendix B)
* Severe pulmonary dysfunction
* Significant hepatic dysfunction (total bilirubin * 30 umol/l or transaminases * 3 times normal level), unless related to myeloma
* Creatinine clearance <30 ml/min
* Uncontrolled diabetes (if receiving antidiabetic agents, subjects must be on a stable dose for at least 3 months)
* History of hypotension or decreased blood pressure (sitting systolic blood pressure [SBP] £100 mmHg and/or sitting diastolic blood pressure [DBP] £60 mmHg)
* Patients with active, uncontrolled infections
* Pre-treatment with proteasome inhibitors
* Current treatment with dexamethasone or proteasome inhibitors
* Patients requiring urgent start of bisphosphonates (e.g. uncontrolled hypercalcemia)
* Have received an experimental drug or used an experimental medical device within 4 weeks before the planned start of treatment
* Contraindications for Magnetic Resonance Imaging ,
see page 9

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	20-08-2008
Enrollment:	25
Type:	Anticipated

Ethics review

Approved WMO

Date:	29-10-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL24539.029.08