Characterizing the bone marrow environment in advanced-stage myelofibrosis. A PET/MRI study.

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Primary objectivesTo characterize the bone marrow microenvironment in advanced stage myelofibrosis (MF) before and during treatment with ruxolitinib, regarding osteoblastic activity, marrow fibrosis and - osteosclerosis and perfusion- and diffusion...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Observational invasive

Summary

ID

NL-OMON43646

Source
ToetsingOnline

Brief title
BEAMY

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
bone marrow fibrosis, Myelofibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Farmaceutische industrie,Novartis

Intervention

Keyword: MRI, Myelofibrosis, PET/CT, Ruxolitinib

Outcome measures

Primary outcome

A detailed description of the bone marrow environment in advanced stage myelofibrosis at baseline and during treatment, using the following parameters:

• Histopathological findings (cellularity, morphology of hematopoietic cells, reticulin and collagen fibrosis, osteosclerosis, vascularity, dilatation of sinusoids) on bone marrow biopsy as scored by the local pathologist

• Functional parameters:

o Perfusion as determined by 15O -water-PET/CT

o Perfusion/permeability as determined with MRI-DCE

o Osteoblastic activity as determined by 18F -fluoride-PET/CT

o Diffusion restriction as determined by MRI-DWIBS

• Conventional treatment response evaluation (reduction in constitutional symptoms / total symptom score (MPN-SAF), reduction of hepatosplenomegaly, improvement in blood hematology values, JAK2 allelic burden and bone marrow abnormalities).

Secondary outcome

Not applicable

Study description

Background summary

In myelofibrosis, it is not yet completely understood how the pathologic alterations in the bone marrow environment evolve. After long-term treatment with ruxolitinib - the present standard therapy for patients with advanced-stage myelofibrosis -, regression of marrow fibrosis has been demonstrated in several patients. The currently used diagnostic tool - the bone marrow biopsy - is however not sensitive enough to detect early and functional changes. In this study we aim to gain more insight into the bone marrow microenvironment in advanced-stage myelofibrosis and changes herein during ruxolitinib treatment, by using well-known imaging techniques. More specifically, we will evaluate osteoblastic activity and bone marrow perfusion and - diffusion characteristics using 15O-water-PET, 18F-Fluoride-PET and MRI-DCE and -DWIBS. Furthermore, bone marrow biopsies will be performed in order to assess histopathological response.

Study objective

Primary objectives
To characterize the bone marrow microenvironment in advanced stage myelofibrosis (MF) before and during treatment with ruxolitinib, regarding osteoblastic activity, marrow fibrosis and - osteosclerosis and perfusion- and diffusion characteristics.
To this end it will be explored:
1. In which manner the balance between fatty red marrow and fibrotic tissue (as assessed with MRI T1- and STIR and histopathological examination) is disturbed, and how it is restored during treatment.
2. a. What the degree of osteoblastic activity (as assessed by 18F-Fluoride-PET) is in advanced stage marrow fibrosis and - osteosclerosis (as assessed by MRI T1, -STIR and histopathological examination)
b. Whether a decrease in osteoblastic activity (as assessed by 18F-Fluoride-PET) during treatment precedes visible regression of marrow fibrosis and - osteosclerosis (as assessed by MRI T1, -STIR and histopathological examination)
3. a. What the degree of diffusion restriction (as assessed by MRI-DWIBS) is in advanced stage myelofibrosis and whether this correlates directly to the presence of marrow fibrosis and/or hypercellularity (as assessed by MRI T1, -STIR and histopathological examination).
b. Whether a decrease in diffusion restriction (as assessed by MRI-DWIBS) precedes visible regression of marrow fibrosis and/or hypercellularity during treatment (as assessed by MRI T1, - STIR and histopathological examination).
4. a. What the degrees of vascular perfusion and permeability (as assessed by 15O-water-PET/CT and MRI-DCE) are in advanced stage myelofibrosis and whether this correlates directly to the presence of hypervascularization and dilatation of sinusoids (as assessed by histopathological examination).
b. Whether a decrease in perfusion and permeability (as assessed by 15O-water-PET/CT and MRI-DCE) precedes visible regression of marrow hypervascularization and dilatation of sinusoids (as assessed by histopathological examination).

Secondary objectives
1. To explore which of the imaging techniques (MRI (-T1, -STIR-, -DCE and -DWIBS) and PET/CT (15O-water-and 18F-Fluoride)) has the greatest value in the diagnosis of myelofibrosis and in response monitoring during ruxolitinib treatment.
2. To explore the degree of sampling error of the bone marrow biopsy in myelofibrosis

Study design

Explorative diagnostic pilot study.

Study burden and risks

For this study, patients will undergo extra diagnostic procedures. Per scheduled appointment at the outpatient clinic, the extra time will amount to 150-180 minutes (510 minutes per patient for the entire study). The extra diagnostic procedures are:
- 9x venapunction (during PET/CT, study protocol page 38)
- 9x intravenous injection (during PET/CT and MRI, protocol pages 33 and 38)
- 2x bone marrow biopsy including - aspirate
- 3x PET/CT (18F-Fluoride, 15O-Water), 8,35-8,85mSv each (dependent on the amount of movement)
- 3x MRI (-T1, -STIR, -DIXON, -DCE, -DWIBS)

The risks of participation are deemed negligible:
- The extra invasive procedures (venapunctions, bone marrow biopsies) carry a very low risk of complications (pain, bleeding) and the complications are well treatable (analgesics, compression).
- The radiation used in the imaging studies is not considered a relevant risk, given the short life expectancy of this group of patients.
- The risk of contrast-allergy is very small, this complication is also well treatable.
- The risk of contrast-nephropathy is small because a screening procedure will be used to determine the need for extra preventive measures in individual patients.
- Incidental findings can be done with the imaging studies, which we will discuss with the participants before study entry.

We believe that conduction of this study is justified because it can lead to better medical care in the future. Momentarily there is little knowledge about the way that pathological changes evolve in the bone marrow of myelofibrosis patients and how they change during therapy. Until now this has been monitored using bone marrow biopsies: an invasive method with proven sampling errors that only provides static information on the bone marrow. It is important that we gain more insight into the dynamic processes that take place. In the future,

this can give rise to more reliable - preferably non-invasive - diagnostic techniques. Also, it might then be possible to demonstrate the influence of a certain treatment on the natural disease course in an earlier stage, which can be of importance in determining duration of treatment (with new and/or often expensive drugs).

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

• A diagnosis of primary-, post-polycythemia vera- or post-essential thrombocythemia MF (according to the 2008 WHO criteria)
• A high- or intermediate-1 or -2 risk level (according to the IWG-MRT DIPSS criteria)
• Fibrosis (grade 2-4) on bone marrow biopsy
• A scheduled treatment with (and thus an indication and eligibility for) ruxolitinib

Exclusion criteria

• Current or previous treatment with a JAK2 inhibitor
• History of allogeneic stem cell transplantation
• Contraindication for treatment with ruxolitinib (including a platelet count < 50,000/µL)
• Contraindication for used imaging modalities
• Inability to sign informed consent

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	02-07-2015
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	17-12-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	02-11-2016
Application type:	Amendment
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	NL50904.029.14