Mast cells and fibrosis in myeloproliferative neoplasms.

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The primary objective is to investigate the role of the hematopoeitic niche and mast cells in the bone marrow of MPN, and the effect of pharmacotherapy on these cells.

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

Summary

ID

NL-OMON48689

Source
ToetsingOnline

Brief title
Mast cells and fibrosis in MPN

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
itching, myeloproliferative neoplasm

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: MPN Stichting,Novartis,Novartis en MPN stichting

Intervention

Keyword: Fibrosis, Mast cells, Myeloproliferative neoplasm, Pruritus

Outcome measures

Primary outcome

There is no single main endpoint in this study. Instead, several parameters of mast cell load and *activity will be evaluated, either separately or combined. Furthermore, these parameters will be compared between patients with/without pruritus, and before and after ruxolitinib treatment.

- Is there an increase of the number of mast cells in the bone marrow of MPN patients? Compare patients with/without pruritus, and compare with patients with multiple myeloma.
- What is the phenotype and function of these mast cells?
* Markers of aberrance (CD2, CD25, CD30)
* Marker of activation (CD63)
* Morphology
* Does this phenotype change during treatment ruxolitinib?
- Is there a relationship between the presence of the JAK2 mutation and pruritus?
- Do MPN patients have higher levels of mast cell mediators in their peripheral blood and if so, do these levels decrease during treatment with ruxolitinib? Do these levels correlate with symptom severity, and specifically with the severity of pruritus?

- Which transcriptional changes can be observed in single cells of the hematopoietic niche (endothelial cells, mesenchymal stromal cells, osteoblast lineage cells) as a driver of bone marrow fibrosis in MPN patients?

Secondary outcome

The effect of ruxolitinib and other pharmacotherapy on the aforementioned parameters.

Study description

Background summary

The spectrum of BCR-ABL negative myeloproliferative neoplasms (MPNs) consists of 3 diseases that are characterized by aberrant proliferation of the myeloid lineage.1 MPNs are commonly associated with activating somatic mutations in the JAK2, CALR or MPL pathway of hematopoietic stem cells (HSC).2
The subsequent proliferation of myeloid cells leads to an overproduction of erythrocytes or thrombocytes and granulocytes resulting in polycythemia vera (PV), essential thrombocythemia (ET) or primary myelofibrosis, respectively. Remodelling of the hematopoietic niche by the MPN-clone and its progeny can lead to secondary myelofibrosis.
Evidence suggests an elevation of proinflammatory cytokines as one of the main contributors to the fibrotic remodeling of the hematopoietic bone marrow.3,4

Over the past years the crucial role of the hematopoietic niche in MPNs have been increasingly elucidated.5 Gli1+ mesenchymal stromal cells have recently been identified by investigators of this proposal to be the major fibrosis-driving cells. Inhibition of these cells leads to a strong reduction of fibrosis as well as clinical burden in vivo.6
The phenotypical and transcriptional changes of these cells during pharmacotherapy with tyrosine kinase inhibitors such as Ruxolitinib are however not yet studied. Treatment with Ruxolitinib has been described to not only ameliorate clinical symptoms in MPN-patients but to also improve the degree of fibrosis.7 Hence, it is clear that the remodeling of the niche responsible for synthesis and deposition of extracellular matrix in myelofibrosis is directly or indirectly influenced by pharmacotherapy.
Unraveling the transcriptional changes in the hematopietic niche will allow us to map the changes induced by pharmacotherapy. Comparing patients with different response rates will enable us to identify mechanisms of resistance and patients at risk that might need to undergo more intense treatment.

Several studies provide evidence pointing to mast cells as an important player in MPN and especially progression to myelofibrosis. An increased number of mast cells as well as the presence of aberrant mast cells is frequently found in the bone marrow of MPN patients.8 There seems to be a correlation between mast cell proliferation and the degree of bone marrow fibrosis in MPN patients.9 As part of the myeloid lineage, mast cells can also harbor MPN specific mutations such as the JAK2V617F substitution leading to an atypical phenotype and function.10 Similar results could also be replicated in JAK2 V617F transgenic mice.11 Furthermore, these mast cells appear *more active* compared to healthy controls. Mast cells in the bone marrow of MPN patients produce more TGF-* and IL-13 in vitro12, and skin mast cells of MPN patients are more easily activated compared with healthy controls13.
Clinically, the numerical and functional aberrancy of mast cells can contribute to symptoms commonly afflicting MPN patients such as fatigue and pruritus.14 Especially severe pruritus has been described to have a significant impact on the quality of life of MPN Patients.
Ruxolitinib has been shown to inhibit mast cell degranulation in vitro. 16 It has been shown to effectively reduce the symptom burden of MPN patients in clinical trials.17,18 It even has been described to ameliorate symptoms in systemic mastocytosis, thereby indicating a relevant effect on atypical mast cells.19,20
In spite of the evidence suggesting a role of mast cells in fibrogenesis, information on the effect of Ruxolitinib on mast cells is scarce. We hypothesize that mast cells are a source of proinflammatory and profibrotic cytokines in the bone marrow, and that Ruxolitinib works at least partly via inhibition of mast cell activation.

Taken together, this study will allow us to map the fibrotic alterations in the hematopoietic niche over the course of therapy in detail and it will enable us to investigate mast cells as therapeutic target and potential driver of myelofibrosis.

Study objective

The primary objective is to investigate the role of the hematopoeitic niche and mast cells in the bone marrow of MPN, and the effect of pharmacotherapy on these cells.

Study design

This is an observational, case-control study performed at the hematology department of the Erasmus MC, IJsselland hospital and Albert Schweitzer hospital. The duration of follow-up will be 3 months, with 2 contact moments for the collection of data (at inclusion and at 3 months).

We will include 62 patients with suspected MPN, or previously diagnosed MPN who

did not receive treatment for the MPN until the moment of inclusion.
Data will be collected at two time points: at inclusion and after three months. For the most main research objectives, we will compare subgroups of patients (e.g. with/without pruritus, or with/without JAK2 mutation). Furthermore, the data obtained at the moment of inclusion will be compared with the data obtained after 3 months. Based on a retrospective search of the MPN cohort of the Erasmus MC in the last three years, we expect that approximately 50% of patients will receive ruxolitinib.

Study burden and risks

Most of the investigations described above (visits to the outpatient clinic, venapunctions, and the first bone marrow punction) are part of the normal work-up of MPN and therefore do not form an extra burden to the participants. The second bone marrow punction and the two questionnaires do form a small study-related burden. The risks of participation are negligible.

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

- Age > 18 years
- Suspected MPN according to WHO criteria (i.e. essential thrombocytosis, polycythemia vera, primary myelofibrosis, or post-ET or post-PV myelofibrosis)
- Previously proven MPN who did not yet receive pharmacotherapy.
- Patient is capable of giving informed consent

Exclusion criteria

- Age < 18 years.
- Previous pharmacotherapy for MPN.
- Intended allogenic stem cell transplantation within 6 months after inclusion.
- Patients after hematopoietic stem cell transplantation

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-02-2019
Enrollment:	62
Type:	Anticipated

Ethics review

Approved WMO Date:	28-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL64166.078.17