Immunological monitoring and assessment of biomarkers predictive of clinical response to first-line treatment with bosutinib or imatinib in chronic phase chronic myeloid leukemia

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Leukaemias
Study type	Observational invasive

Summary

ID

NL-OMON42791

Source
ToetsingOnline

Brief title
Biomarker substudy for Bfore protocol

Condition

- Leukaemias
- Leukaemias

Synonym
Chronic myeloid leukemia; CML

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Universiteit van Helsinki;Finland

Intervention

Keyword: Biomarker, CML, immunological monitoring

Outcome measures

Primary outcome

The primary endpoint is to define whether bosutinib and /or imatinib therapy induces numerical or functional changes in the immune effector cells as assessed by flow cytometry and functional assays of peripheral blood samples.

Secondary outcome

The secondary aims of the study are: (a) to correlate the immunological effects of therapy with achievement of major molecular response at 12, 18 and 24 months and with achievement of MR4.0 and MR4.5 at 12,18 and 24 months. (b) To correlate the immune cell profile at diagnosis with early molecular response (BCR-ABL % IS) at 3 months. (c) To find biological markers which can predict the response to TKI therapy, and possibly also which patients are able to discontinue the therapy without disease relapse. (d) To assess the leukemia stem cell (LSC) burden at diagnosis and after 3 months of therapy by flow cytometry and correlate that to therapy response and hematological toxicity. (e) To identify novel CML LSC markers by a comprehensive antibody screen and RNA sequencing. This includes assessment of leukotriene and DNA repair signaling. (f) To analyse phosphoprotein signalling both in CD34+ and mononuclear cell fractions and study the effect of bosutinib and imatinib on it

and correlate the phosphoprotein profile to clinical responses.

Study description

Background summary

CML is currently treated successfully with tyrosine kinase inhibitors (TKIs), which inhibit the growth of leukemic cells. It has previously been thought that TKI-treatment is life-long, however, a few recent studies have shown that some patients can successfully discontinue TKI treatment and be cured. The mechanisms of cure are still unknown. It can be related to improved capacity of the immune system to detect and kill leukemic stem cells.
It has been suggested that certain TKIs can act on the immune system by modulating the body*s own white blood cells. In this substudy, we will investigate the immunomodulatory effects of bosutinib and imatinib during the treatment of CML and the different features of leukemic stem cells.

Study objective

In this laboratory study, we will examine the properties of leukemic stem cells and the immuno-modulatory effects of bosutinib and imatinib in newly diagnosed chronic phase CML patients. Further, we aim to study whether they have an impact on the therapy response.

1) To define the immune cell phenotype and function in untreated CML patients and correlate that with the therapy response.

2) To study whether bosutinib and/or imatinib therapy induces numerical or functional immunological changes as assessed by flow cytometry and functional assays of peripheral blood samples at 3 and 12 months time points after the therapy start.

3) To characterize the leukemic stem cell population with the novel markers and methods in untreated CML patients.

Study design

This is a substudy to the clinical multicenter trial *A Multicenter Phase 3 Randomized Open Label Study of Bosutinib versus Imatinib in Adult Patients with Newly Diagnosed Chronic Phase Chronic Myelogenous Leukemia* (AV001, Eudract #2013-005101-31).

Peripheral blood samples will be collected at diagnosis and at 3 and 12 months after the start of therapy.

The immunophenotype, clonality and the function of cells will be analyzed.

In addition, bone marrow samples will be collected from untreated CML patients and at 3 months after start of therapy. Leukemic stem cells will be assessed from bone marrow samples, in part by using novel markers and methods

30 patients will be included; 15 in the bosutinib arm and 15 patients in the arm with imatinib.

Study burden and risks

Blood and bone marrow sample collection occurs according to normal routine procedures and no special safety aspects are foreseen.
Results from this study can improve our understanding of CML, but the substudy is not directly beneficial to the patient.

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

1. Molecular diagnosis of CP CML of <= 6 months (from initial diagnosis).
• Diagnosis of CP CML with molecular confirmation by detection of BCR-ABL rearrangement at screening (cytogenetic assessment for Philadelphia chromosome is not required for enrollment); diagnosis of CP CML will be defined as all of the following:
a) <15% blasts in peripheral blood and bone marrow;
b) <30% blasts plus promyelocytes in peripheral blood and bone marrow;
c) <20% basophils in peripheral blood;
d) >=100 x 109/L platelets (>=100,000/mm3);
e) No evidence of extramedullary disease except hepatosplenomegaly; AND
f) No prior diagnosis of AP or BP-CML.
• Philadelphia chromosome status will be identified at screening. Both Ph+ and Ph- patients may be included.
2. Adequate hepatic and renal function defined as:
• AST/ALT <=2.5 x upper limit of normal (ULN) or <=5 x ULN if attributable to liver involvement of leukemia.
• Total bilirubin <=2.0 x ULN (unless associated with Gilbert*s syndrome).
• Creatinine <=1.5 x ULN.
3. Able to take oral tablets.
4. ECOG performance status of 0 or 1.
5. Age >=18 years.
6. Negative serum pregnancy test within 2 weeks of the first dose of study drug if the patient is a woman of childbearing potential. A woman of childbearing potential is defined as a woman who is biologically capable of becoming pregnant. This includes women who are using contraceptives or whose sexual partners are either sterile or using contraceptives. Patients and patient's partners of childbearing potential (physically able to have children) and who are sexually active, must agree to use birth control consistently and correctly during the study and for at least 28 days after they have stopped taking the study drug.
7. Ability to provide written informed consent prior to any study related screening procedures being performed.

Exclusion criteria

1. Any prior medical treatment for CML, including TKIs, with the exception of hydroxyurea and/or anagrelide treatment.
2. Any past or current CNS involvement, including leptomeningeal leukemia.
3. Hypersensitivity to the active substance or to any of the following excipients: microcrystalline cellulose (E460), croscarmellose sodium (E468), poloxamer 188, povidone (E1201), magnesium stearate (E470b), polyvinyl alcohol, titanium dioxide (E171), macrogol 3350, Talc (E553b), iron oxide red (E172).
4. Extramedullary disease only.

5. Major surgery or radiotherapy within 14 days of randomization.
6. Concomitant use of or need for medications known to prolong the QT interval.
7. History of clinically significant or uncontrolled cardiac disease
8. Known seropositivity to human immunodeficiency virus (HIV), current acute or chronic hepatitis B (hepatitis B surface-antigen positive), hepatitis C or evidence of decompensated liver disease or cirrhosis.
9. Recent or ongoing clinically significant GI disorder, e.g. Crohn*s Disease, Ulcerative Colitis, or prior total or partial gastrectomy.
10. History of another malignancy within 5 years with the exception of basal cell carcinoma or cervical carcinoma in situ or stage 1 or 2 cancer that is considered adequately treated and currently in complete remission for at least l2 months.
11. Uncontrolled hypomagnesemia or uncorrected hypokalemia due to potential effects on the QT interval.
12. Current, or recent (within 6 months), participation in other clinical trials.
13. Women who are pregnant, planning to become pregnant during the study or are breastfeeding a child, or men who are planning to father a child during the study.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2015
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO

Date:	19-05-2015
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	NL52748.029.15