To study the effects of anti fungal treatment of a subset in CLL patients harboring stereotypic receptors with high specificity for yeasts and molds.

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To test the hypothesis that CLL depend on their cognate BCR ligands for growth and/or survival and that lowering specific antigenic pressure decreases the activation status of the leukemia clone resulting in a decrease in tumor burden.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON36874

Source
ToetsingOnline

Brief title
posaconazole Study

Condition

- Leukaemias

Synonym
posaconazole; CLL

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: anti fungal treatment, CLL, posaconazole

Outcome measures

Primary outcome

* Decrease in clone size

* Decrease in activation status of CLL cells

Secondary outcome

not applicable

Study description

Background summary

B-cell chronic lymphocytic leukemia (CLL), the most common leukemia in western adults1, is an incurable clonal expansion of CD5+CD19+ B lymphocytes. The B-cell receptor (BCR) has a prominent role in the pathogenesis of this disease, indicated by the prognostic value of the somatic hypermutation (SHM) status of the immunoglobulin (Ig) heavy chain variable gene (IGHV)2,3. Over 30% of CLL cases can be grouped in subsets based on the stereotypic complementary determining region 3 (CDR3) amino acid sequences of the expressed IGHV1, 4-9, strongly suggesting that BCR recognition of particular antigens is instrumental for oncogenic transformation. In a recent study, it was reported that CLL have ongoing BCR-signaling within proliferation centers10, suggesting that recognition of particular antigens may drive tumor expansion.
We recently discovered a new CLL homology subset expressing mutated IGHV3-7 rearrangements paired to IGKV2-24 encoded light chains. We show that these stereotypic BCRs are highly specific for a carbohydrate structure, abundantly present in the cell wall of commensal yeasts and molds. Moreover, CLL cells expressing these stereotypic receptors are induced to proliferate in the presence of this natural ligand. To our knowledge, this study is the first to establish a group of common pathogens as functional ligands for BCRs of B-cell lymphomas and provides a rationale for antigen-targeted therapies.

Study objective

To test the hypothesis that CLL depend on their cognate BCR ligands for growth and/or survival and that lowering specific antigenic pressure decreases the activation status of the leukemia clone resulting in a decrease in tumor burden.

Study design

Three patients, harboring a CLL with mutated IGHV3-7 rearrangements paired to IGKV2-24 encoded light chains with proven reactivity to yeast and moulds, will be treated for six weeks with posaconazole. Posaconazole levels will be measured every two weeks (2 time points). Before treatment, immediately after treatment and 30 days after treatment blood will be drawn for laboratory analysis.

Intervention

Patients have to take 3 times daily one tablet of posaconazole for a period of six weeks

Study burden and risks

Patients have to take 3 times daily one tablet of posaconazole for a period of six weeks. Blood needs to be drawn at 5 time points.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Diagnosis of CLL / MBL with mutated IGHV3-7 rearrangements paired to IGKV2-24 encoded light chains;
* Age 18-80 years
* No CLL related treatment during the last 3 months;
* Able to adhere to the study visit schedule and other protocol requirements;
* WHO performance status of * 2;
* Laboratory test results within these ranges: absolute neutrophil count * 1.0 x 109/l, platelet count * 30 x 109/l, creatinine clearance * 60 ml/min, total bilirubin * 25 µmol/L, AST & ALT * 2 x ULN;
* Written informed consent.

Exclusion criteria

* Known hypersensitivity and/or serious adverse reactions to posaconazole or similar drugs
* Concomitant anti-yeast/mould medication;

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	posaconazole
Generic name:	Noxafil
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	16-07-2012
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
EudraCT	EUCTR2012-002041-38-NL
CCMO	NL40610.018.12