Comparative genomics and receptor signaling in MBL and CLL arising in siblings

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

Summary

ID

NL-OMON41246

Source
ToetsingOnline

Brief title
MBL - CLL

Condition

- Leukaemias

Synonym
Monoclonal B-cell lymphocytosis, white blood cells without clinical relevance

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: CLL, MBL, receptor signaling

Outcome measures

Primary outcome

1) Definition of genetic differences between MBL en CLL as detected by whole

exome sequencing and SNP microarray analysis

2) Detection of antigen-independent BCR signaling in MBL en CLL.

Secondary outcome

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Study description

Background summary

Chronic lymphocytic leukemia (CLL) is a monoclonal expansion of functionally incompetent B lymphocytes with a distinct phenotype. CLL amounts to 16.5 % of all newly diagnosed lymphomas and has the highest prevalence of all hematologic tumors. 30-40% of CLL patients will die of their disease, and CLL remains incurable with conventional therapy. Therefore, novel treatments are required to improve the outcome of CLL, but their development is hampered by the fact that the etiology of CLL has remained elusive.
Monoclonal B-cell lymphocytosis (MBL) is a clonal expansion of B cells of mostly CLL phenotype but without fulfilling diagnostic CLL criteria. The prevalence of MBL in adults is 2-6% and in relatives of CLL patients 14-18%. 15-20% of MBL eventually progress to CLL.

Study objective

This project aims to achieve advances in understanding CLL initiation and progression, and to identify novel targets for therapy of CLL, through a detailed genetic and immunological comparison of manifest CLL and MBL as the premalignant counterpart.

Study design

Screening for MBL in siblings of CLL patients is performed by standardized

four-color flow cytometry.
In the first work package, the B-cell receptor (BCR) expressed by CLL and MBL cells is being amplified by PCR and cloned.
The signaling properties of CLL and MBL BCR are tested for antigen-independent, autonomous signaling in murine pre-B cells deficient in Rag2, Vlambda5, and BLNK (SLP-65).

The second work package aims to identify genetic aberrations in MBL with the highest possible resolution by whole exome sequencing and SNP microarrays. Restriction of this analysis to CLL and MBL arising in siblings will reduce irrelevant genetic differences such as copy number variations that exist between nonrelated individuals as much as possible. We anticipate that some identifiable genetic aberrations are associated with the premalignant MBL state, including some CLL-associated genetic aberrations, but that an individual MBL will carry less genetic changes than an average CLL. Identified genetic changes will be validated on an existing cohort of 250 CLL cases.

The aim of the project is to deduce an integrated and hierarchical model of CLL etiology by ranking genetic and signaling events as obtained from both work packages. This model will perform an instrumental role in developing rational, biology-based approaches to prevent CLL progression and to control the established malignancy.

Study burden and risks

A single venapuncture to collect a blood sample of 45 ml. The risk for deleterious side effects is 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

diagnosis of CLL
or
a sibling with CLL

Exclusion criteria

n.a.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	16-02-2015

Enrollment:	232
Type:	Actual

Ethics review

Approved WMO Date:	31-01-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	24-04-2014
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	15-07-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	NL39919.058.12