Mutational analysis of extranodal marginal zone lymphoma of mucosa associated lymphoid tissue (MALT lymphoma) in the salivary gland of patients with Sjögren*s syndrome: identification of driver mutations and therapeutic targets

Published: 10-02-2017
Last updated: 14-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Observational invasive

Summary

ID

NL-OMON43147

Source
ToetsingOnline

Brief title
Mutational analysis of ENMZL associated with Sjogren syndrome.

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Lymphoid cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Local funding

Intervention

Keyword: MALT lymphoma, Mutational analysis, Sjogren disease

Outcome measures

Primary outcome

Detection of recurrent mutations in MALT lymphoma associated with Sjogrens

disease.

Secondary outcome

n.a.

Study description

Background summary

Sjögren*s syndrome is an autoimmune disease characterized by dry mouth and eyes. Patients have a 5% risk of developing a B-cell lymphoma in the salivary gland. It is largely unknown which genetic changes result in the development of these lymphomas. By using novel techniques (next generation sequencing) we will try to establish the basis for the development of these lymphomas.

The UMCG is an expertise center for Sjögren*s syndrome (SS) and ± 40 new patients are seen annually. SS is a chronic multisystem autoimmune disease characterized by diminished lacrimal and salivary gland function associated with lymphocytic infiltration of the secretory glands. In patients with SS salivary gland enlargement can vary over time, but persistent enlargement should raise the suspicion of a B-cell lymphoma (B-NHL) which develops in 4-7% of patients. The marginal zone B-cell lymphoma (MZL) of mucosa associated lymphoid tissue (MALT lymphoma) constitutes 48%-75% of B-cell lymphoma (B-NHL) in SS.
The development of SS MALT lymphoma follows after an initial period of

polyclonal B-cell proliferation in the exocrine tissue. Sustained (auto) antigen stimulation and inflammation can induce oncogenic events, e.g. through reactive oxygen species, resulting in genetic instability of B-cells. Over time, multiple disturbances in B-cell differentiation and trafficking result in oligo-monoclonal B-cell expansion. A current research project at the Department of Rheumatology and Clinical Immunology sponsored by the Dutch Arthritis Foundation tests the hypothesis that the MALT lymphoma develop from a relatively small subset of intraepithelial B-lymphocytes (1)
Relatively little is known about the genetic aberrations that underlie the development of SS MALT lymphoma. In non-SS MALT lymphoma several chromosomal translocations can occur. The frequency of translocations t(11;18), t(1;14), t(14;18) and t(3;14) vary depending on the anatomical localization. These translocations have in common that they result in constitutive activation of the nuclear factor-kappa-B (NF-kB) pathway. In SS MALT lymphoma only trisomies 3, 12 and 18 can be found at low frequency (2). The majority of SS MALT lymphomas lack any recognizable recurrent chromosomal alteration. Currently there is very limited data on the mutational landscape of SS and non-SS MALT lymphoma (3). These studies so far indicate that TNFAIP3, a regulator of the NF-kB pathway might play a role in the pathogenesis of MALT lymphomas.

Study objective

1. We will perform an exploratory study using whole exome sequencing (WES) on SS MALT lymphoma samples to pick up specific gene mutations enriched or exclusively present in salivary MALT lymphoma in SS patients.
2 .We will investigate the relation between mutational load and SS disease activity and whether there is enrichment for deleterious mutations in patients with a high SS activity as compared to low SS activity.
3. We will perform (targeted) exome sequencing on repetitive tumor samples of patients to evaluate clonal evolution in order to detect deleterious mutations early in the course of the disease in minor sub clones.

Study design

Mutational analysis will be performed on a pilot serie of 10-15 patients using next generation sequencing of tumor samples and germline DNA. If specific mutations are found the research will be extended to 30 patients to validate the incidence of these mutations within the MALT lymphoma patients.

Study burden and risks

No risk for participating patients.

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

Patients previously diagnosed with a MALT lymphoma

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:	Recruitment stopped
Start date (anticipated):	10-02-2017
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	10-02-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL58950.042.16