Clinical Key Note Lecture

Clinical impact of early lymphoma lesions

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Overview of my clinical talk

- MGUS
- MBL (MLUS)
- CLL
- Follicly
- MALT
- MCL
- Virus driven lymphoma
  - HVC
  - EBV
    - PTLD
    - Transformation
Lymphomas – heterogenous diseases
some are early lesions

- Morphology
- Phenotype
- Chromosomal aberrations
- Mutational status
- Prognostic markers
- Clinical picture
Early lesion or disease?

Neoplastic cell
Tumor
Clonality & Genetic aberrations

In situ or partially involved

Micro (and macro) environment

How to follow-how to treat?
Predictive marker for progress

Conventional prognostic markers
FLIPI, MIPI, Rai, Binet

How to follow - how to treat?

Prognosis is dependant on type of follow-up, is therapy required?
The most effective therapy!
Incipient myelomatosis or essential hyperglobulinemia with fibrogenopenia

A new syndrome?

- Oronasal bleeding
- Lymphadenopathy
- Anemia and thrombocytopenia
- Elevated erythrocyte sedimentation rate (SR)
- Hyperviscosity
- Lymphoid cells and mast cells in bone marrow

Acta Med Scand 1944
Diagnostic criteria for WM

- Bone marrow infiltration
  small lymphocytes with lymphoplasmacytic features*
  predominantly intertrabecular pattern (bone marrow biopsy)

2. Typical immunophenotype

- IgM monoclonal gammopathy
  ----- *irrespective* of Ig M concentration

* According to the WHO classification
WM is a lymphoplasmacytic lymphoma

*International Workshop WM*
Athens 2002
Paris 2004
Stockholm 2008
IgM-Monoclonal gammopathy of undetermined significance (IgM-MGUS)

- Serum monoclonal IgM < 3g/dl
- *No morphological evidence of bone marrow infiltration* (immunophenotypic and/or molecular evidence of clonality may be found)
- *No symptoms* or signs attributable to IgM or to tumor infiltration
M-spike in serum requires a clinical evaluation and a close follow-up - wait and watch.

Morphology

- Lymphocytosis

Differential diagnosis:
- Splenic marginal zone lymphoma

Splenomegaly
Predictors for progress

6q deletion (gene: BLIMP-1)

- May distinguish IgM-MGUS from WM
- May have prognostic significance more aggressive clinical features

6q deletion (gene: BLIMP-1)

- 7% by conventional cytogenetics
- 34% by FISH

wait and watch

- Guidelines
  - Careful clinical evaluation
  - Information
    Patient, family, insurance company
  - This is not a cancer
  - Follow-up
Monoclonal B-cell lymphocytosis (MBL)

Discussed by Paolo Ghia

50% adults > 90 years of age

MLUS (Monoclonal lymphocytosis of undetermined significance)

MGUS: monoclonal gammapathy of undetermined significance
Monoclonal B lymphocytes with characteristics of "indolent" CLL

Distinctive phenotype (4-colour flow)

3.5% of 910 adults (> 40 years of age)

Rawstron et al, Blood 2002
B-CLL diagnostic criteria

Accumulation of small lymphocytes "mature appearing"

Dameshek 1981

2008 IWCLL guidelines:
• Lymphocytosis $>5 \times 10^9$/L (in blood)
• Specific clonal B-cell phenotype

MBL: Lymphocytosis $<5 \times 10^9$/L (in blood)
Continuum with CLL
Monoclonal B-cell lymphocytosis

✓ 1520 patients (60-80 years): < 5000 ly/mm³
  - CLL phenotype in 78 (5.2 %)
✓ 2228 patients with current or previous lymphocytosis - CLL phenotype in 309 (13.9 %)

Longitudinal cohort:
• 185 patients with MBL (< 5000 ly/ mm³)

Monoclonal B-Cell lymphocytosis
Median follow-up: 6.7 years (range: 0.2-11.8)

Lymphocyte Count increased to > 10,000 cells/mm³

*95% CI.

Rawstron AC, et al.
Prognostic factors in MBL
Sterotyped receptors in 4.5% of cases
Ghia et al.(yesterday)

Maddocks-Christianson K, et al. Ghia et al
MBL clinical view

- A precursor state for CLL?
- Yes, 1% /year!

- Number of cells with CLL phenotype will predict progression

- Related to CLL in a similar way that MGUS is related to myeloma?

Clinical MBL? MLUS? Cancer ??
Some lymphoma sites are not easy to detect

Mediastinal
Para-aortal
Mesenterial
Retroperitoneal

Splenomegaly
Hepatomegaly
CT abdomen in a MBL? patient
Bulky nodal disease

Before therapy

Post therapy
B-CLL clinical features

✓ Asymptomatic at diagnosis: 70%–80%
✓ Some patients will never need therapy and survival not affected
✓ Spontaneous remission in a few
✓ Other patients have an aggressive disease with short survival
Immune incompetence - infections- hemolysis

• B-CLL B cells poor antigen presenting cells (APCs)
  Defect antigen presentation

• Anergic B-CLL cells
  Hypogammaglobulinemia
  • Monoclonal low-affinity IgM autoantibodies
  • Polyreactive IgG autoantibodies
  hemolysis (DAT+)
CLL

- Incidence: 3 (2-4.5) /100 000/year *
  - >70 years: 50 /100 000/year
  - Median age: 65–70
- The incidence increasing in younger
- 20–30% diagnosed < 55 years

Incidence dependent on the cut off value for lymphocyte counts
Conventional prognostic factors

• Clinical staging Rai, Binet

• Lymphocyte doubling time (LDT)

• Pattern of marrow involvement

• Serum markers: LDH, beta2-microglobulin, thymidine kinase, sCD23, sCD54, sCD20
CLL: prognosis
CLINICAL STAGE, RAI SYSTEM

Rai et al 1975
Prediction of prognosis in CLL
Genomic aberrations by FISH

Döhner et al NEJM 2000;343:1910-6
Microenvironment

CLL

Endothelial/Stromal cells

NK-cells

“Nurse-like” cells

PDGF

VEGF

TNF-α

IL-6

CD4+ CD8+ T-cells
Wait and watch Chlorambucil in "indolent" CLL
French Cooperative Group

Two randomized trials (n=609, n=926)

In the untreated group:

• 49% of pts did not need therapy after FU of >11 years

• To defer therapy until the disease progresses to stage B or C did not compromise survival

German CLLSG CLL8 study first-line R-FC

Median observation time 25.5 months

R-FC: median PFS 42.8 months

FC: median PFS 32.3 months

\( p = 0.000007 \)

Hallek et al. ASH 2008, Abstract 325.
CLL8 Genetic Analyses: PFS

Stilgenbauer et al. ASH 2008 Abstract 781.
CLL8 Treatment Effect: PFS

11q- group
P<.001
Evaluation of CLL patients

- CT thorax, abdomen (abdominal ultrasound)
- Pulmonary X-ray (considering future therapy complications)

If progress and therapy requiring disease
- Bone marrow biopsy
- FISH: 11q-, +12, 13q-, 17p-
- (IGVH-gene mutation status)
Mantle cell lymphoma

- A clinically aggressive disease with short survival
  - Common variant (small cell type)
  - Blastic variant: 10%
  - Blastoid transformation 30%
  - High proliferation
  - t(11;14), Cyklin D1
  - del11q 22-23 and/or del/mut17p
Indolent MCL

• Often leukemic with splenomegaly
• Associated with MZL or CLL in some cases
• Sox11 negativity

• "Indolent" need a long term follow-up
  - until then - clinical judgment
In situ MCL

• In situ MCL (in more than one site)
  – Some SOX11+(44%)

• Some healthy person with t(11;14)
• 5/6 (83%) had both t(11;14) and t(14;18)
  – Lecluse et al. Leukemia 2009
Predictive marker for progress

SOX 11?

Proliferation

Which compartment?

Microenvironment

How to follow-how to treat?
Risk faktors for lymphoma

- Chronic antigen stimulation
- Autoimmunity
- Infections
- Immunedeficiency
  - congenital /acquired

- Donor derived MCL and CLL
- described after allo transplantation
<table>
<thead>
<tr>
<th>Microbial pathogen</th>
<th>WHO Histologic subtype</th>
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<tbody>
<tr>
<td>EBV</td>
<td>Hodgkin’s disease</td>
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<td>Polymorphic PTLD</td>
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<td>Burkitt’s lymphoma</td>
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<td>Monomorphic PTLD (DLBCL)</td>
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<td>Primary effusion lymphoma (with HHV8)</td>
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<td>HHV8</td>
<td>Primary effusion lymphoma</td>
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<td>Plasmablastic lymphoma (DLBCL)</td>
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<td>PTLD (rare)</td>
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<td>HCV</td>
<td>SLVL (splenic MZ-lymphoma)</td>
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<td>Other marginal zone lymphoma</td>
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<td></td>
<td>DLBCL</td>
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<td><strong>H. pylori</strong></td>
<td>Gastric MALT-lymphoma (extranodal MZ-lymphoma, MALT type)</td>
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<td><strong>C. jejuni</strong></td>
<td>IPSID (extranodal MZ-lymphoma, MALT type)</td>
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<td><strong>B. burgdorferi</strong></td>
<td>Primary cutaneous B-cell lymphoma (various WHO subtypes including extranodal MZ-lymphoma, MALT type)</td>
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<td><strong>C. psittaci</strong></td>
<td>Ocular adnexal lymphoma (extranodal MZ-lymphoma, MALT type)</td>
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<td><strong>HTLV-1</strong></td>
<td><strong>HTLV-1 related Adult T cell Leukemia/lymphoma</strong></td>
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Helicobacter pylori

MALT lymphoma

7q32 deletion, MiR 182 (20%)
Therapy for MALT (mucosa associated lymphoid tissue)

*H. Pylori* eradication

CR: 60% - 80%

Long response duration
Molecular remission!!

If disseminated disease:
- anti-CD20 mAbs+ cytostatics
Marginal zone lymphoma (MZL)

Indolent disease often disseminated

Gastro-intestinal  Lung  Skin  Thyroid
Chronic antigen stimulation

- Thyroid
  Hashimoto thyroiditis
- Salivary gland
  Myoepithelial sialoadenitis +/- Sjögren S.
- Lung
  Lymphoid interstitial pneumopathy
Ocular Adnexal Lymphoma (OAL)

- Chlamydia Psitacci?
Cutaneous marginal zone lymphoma

- Paplers, plaques or noduli
- Solitary or multiple

Borellia Burgdorferi?
Follicular lymphoma (FL)

\[ t(14;18) \ (q32;q21) \]

BCL-2 anti-apoptotic protein

NORMAL follicle → LYMPHOMA → Transformation

Aggressive lymphoma

\( p16 \)

\( p53 \)

\( c\text{-myc...} \)
Definition of FL

FLIS (Follicular lymphoma in situ)
Partially involved lymph node
One node?
One compartment?
Definition of FL- grade (WHO)

The number of centroblasts (CB) per high power field in 10 neoplastic follicles

- Grade 1: 0–5  Indolent disease
- Grade 2: 6–15
- Grade 3: >15  Aggressive?

Distinction 3a and 3b
WHO classification 2008
FDG-PET in a patient with FL grade 2

Before therapy  After 2 courses  After 4 courses

Prognostic factors in FL

- Grade 1, 2, 3a (3b) FLIS? Partial involvement?
- “GEP signatures”
- Microenvironment
- FLIPI
- GELF-criteria high tumor burden
Gene microarray
‘immune response signatures’ with
prognostic significance in FL

• **Survival** following diagnosis of FL is predicted by molecular features of *non-malignant* tumour-infiltrating immune cells

Lymphoma/leukaemia molecular profiling project¹,²

Microenvironment

Th2

Treg

CD8

Th1

MF

STAT1

MF

FL

FDC

DC

NK
Follicular Lymphoma International Prognostic Index (FLIPI)

- Age (<60 years vs ≥60 years)
- Hb (≥12 g/dL vs <12 g/dL)
- LDH (normal vs abnormal)
- Stage (I/II vs III/IV)
- Number of nodal sites (≤4 versus >4)
Bulky disease???
FLIPI survival

- **Surival probability**
- **Months**
- **0-1** Good
- **2** Intermediate
- **3-5** Poor

Survival probability decreases over time, with different lines representing different FLIPI survival categories.
Watchful waiting vs chemotherapy (chlorambucil) BNLI trial (n= 309)

- Median follow-up: **16 years** (from **1981**)

- Median time to need of chemotherapy in the watch and wait arm: **31 months**

- Actuarial chance of not requiring chemotherapy at ten years: **19%**

  Ardeshna K. et al The Lancet 2003
Watch and wait still an option?

1) rituximab  (stopped July 2007)
2) rituximab+ maintenance
3) watch and wait

Principal Investigators:
Kirit Ardeshna  David Linch, London
SUMMARY
Early lesions? Incipient lymphoma?
Biologically interesting!
Wait and watch?? Rebiopsy!