How I treat patients with Waldenström’s makroglobulinemia

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Roche, Mundipharma, Jansen

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Incipient myelomatosis or essential hyperglobulinemia with fibrinogenopenenia

- Oronasal bleeding
- Lymphadenopathy/enlarged lymph nodes
- Anemia and thrombocytopenia
- Hyperviscosity
- Elevated erythrocyte sedimentation rate (SR)
- Lymphoid cells and mast-cells in bone marrow
- Ultracentrifuge: large globulin

Today: Waldenström`s Makroglubulinemia (WM)

Waldenström J. Acta Med Scand 1944
Symptoms in WM-patients

- Anemia/thrombocytopenia
  - Relative anemia (high plasmavolume)
- Lymphadenopathy
- B-symptom
- Hyperviscosity
- Cryoglobulinemia
- Cold agglutinin disease
- Neuropathy
- Amyloidosis
WM – diagnostic criteria

International Workshop on WM

- Athens 2002*
- Paris 2004
- Stockholm 2008
- Venice 2010
- Newport 2012
- London 2014

*Owen RG, et al. Clinicopathological definition of WM
Semin Oncol. 2003

According to the WHO-classifikation 2008:
“WM is a lymphoplasmacytic lymphoma”
WM – diagnostic criteria

Bone marrow infiltration
- Small lymphoplasmacytic lymphocytes
- Intertrabecular growth
- Typical immunophenotype
- Microenvironment
  T-cells, dendritic cells, mast cells
  - Coculture of mast cells with WM cells leads to cell proliferation

✓ Biopsy with immunohistochemistry (IHC)
✓ Aspiration and flow-cytometry
WM immunophenotype

Positivity for

Light chain restricted IgM

CD19, CD22, (dim), CD25, CD27, CD52 and CD20

CD5 positivity in 5-20% of all cases

Negativity for CD10, CD23, CD103 och CD138

A subclone, mostly plasmacells, are CD20-negative and CD138-positive
M-spike in serum required for WM

Irrespective of IgM concentration

Splenomegaly + IgM spike

Differential diagnosis:
Splenic marginal zone lymphoma
CD22+ and CD11c+

MYD88 mutations status
Diagnostic value
- Marginal zone lymphoma (7-10%)
- IgM-myeloma
- CLL with plasmacytic/cytoid differentiation (4%)
MYD88 L265P mutation in WM

✓ **Whole genome sequencing** of lymphoplasmacytic cells from 30 WM-pts (paired normal tissue sequencing in 10 pts)

✓ A recurring sequence variant on **chr 3p22.2** identified with a single nucleotide change in the myeloid differentiation primary response gene (**MYD88**)

✓ **Sanger sequencing confirmed the MYD88 L265P** variant in tumor samples from 26 patients

Treon SP, Xu L, Yan G et al. NEJM. 2012;367:26-33
### Diagnostic criteria (Mayo):

<table>
<thead>
<tr>
<th>IgM MGUS</th>
<th>Asymtomatic WM</th>
<th>Symtomatic WM</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-component, type IgM &lt; 30g/L, and/or</td>
<td>M-component, type IgM ≥30g/L, and/or</td>
<td>M-component, type IgM ≥30g/L, and/or</td>
</tr>
<tr>
<td>LPL in BM &lt;10%</td>
<td>LPL in BM ≥10%</td>
<td>LPL in BM ≥10%</td>
</tr>
<tr>
<td>No WM related symtom*</td>
<td>No WM related symtom</td>
<td>WM related symtom or end-organ failure*</td>
</tr>
</tbody>
</table>

* B-symtom, anemia, hyperviscosity, lymphadenopathy/hepatosplenomegaly

IgM MGUS: 10-87% show MYD88 L265P mutation - higher risk of “malignant evolution”
Other risk factors

6q21 deletion (BLIMP-1 gene)

- 10% conventional cytogenetic
- 34% FISH

Associated to aggressive clinical features
**C-X-C chemokine receptor type 4 (CXCR4)**

- **Somatic ”WHIM-syndrome like” CXCR4 C1013G mutation**
  - in 20-30 % of WM cases

  The CXCR4 plays a role for cell trafficking of
  - hematopoietic stem cells
  - clonal B-cells

  CXCR4 WHIM mutation is related to
  - high tumor proliferation
  - extramedullary dissemination
  - decreased survival in WM patients

Roccaro AM et al, Blood. 2014;123:4120-31
Important tests before therapy

• DAT = direkt antiglobulin test
  – Sampling in 37 degrees for coldagglutinins

• Cryoglobulin (sampling in 37 degrees)

• Hepatitis C serology

• Serum viscosity (if M-komponent >40g/L)?

• P-FLC = free light chains?
When to treat?

Serum IgM is not an indication for treatment

- Anaemia/thrombocytopenia
- Adenopathy/organomegaly
- Hyperviscosity
- Cryoglobulinaemia
- Cold agglutininemia
- Neuropathy
- Amyloidosis
- Transformation

Watch and wait
Asymptomatic WM – do not treat

- Any size of serum IgM MC
- Any degree of BM-LP infiltration
- No symptoms attributable to IgM or MC/tumour infiltration
### Prognostic factors at the time of therapy
The International prognostic Scoring System for WM (ISSWM)

<table>
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<tr>
<th>Risk group</th>
<th>Adverse covariates*</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Low</strong></td>
<td><strong>1</strong> (except age)</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>2</td>
<td>or only age &gt; 65 years</td>
</tr>
<tr>
<td><strong>High</strong></td>
<td>&gt; 2</td>
<td>36%</td>
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</table>

*Adverse covariates:
- IgM $> 70$ g/l
- $\beta_2$M $> 3$ mg/l
- Hb $\leq 11.5$ g/dl
- Plts $\leq 100 \times 10^9$/l
- Age $> 65$ years

Treatment options for WM

**Single agents**
- Rituximab (standard or extended schedule)
- Cladribine/fludarabine
- Chlorambucil
- Bortezomib

**Rituximab-based combinations**
- R + fludarabine/cladribine/pentostatin + cyclophosphamide
- R + bendamustine
- R + cyclophosphamide + dexamethasone (DRC)
- R+ bortezomib

Treatment recommendations by International Workshops on WM.
Single-agent therapy

- Low Ig M and cytopenias
- High Ig M - risk of "flare"
- Old age and slow progression

Plasmapheresis

Single-agent rituximab

Single-agent chlorambucil
Plasmapheresis for removal of IgM

✓ Hyperviscosity-related symptoms

✓ Prevention
  ✓ Reduce IgM before rituximab

✓ **Reversing** (rapid effect needed)
  ✓ Headache, breathlessness
  ✓ Retinopathy
  ✓ Venous dilatation
  ✓ Bleeding
  ✓ Anemia
WM 1- prospective randomized trial

Previously untreated WM (339), MZL(37) and LPL

Median age: 68 years (40-89)

NCRI Lymphoma Clinical Studies Group (UK)
Groupe d’Etudes sur la Leucémie Lymphoïde Chronique et la maladie de Waldenström (France)

WM 1- prospective randomized trial
07/01-12/09 (n=414)

- Chlorambucil: 8 mg/m2 x10 days/28 days
  (max 12 cycles)
  CR+PR: 38.6%

- Oral Fludara: 40 mg/m2 orally x5 days/28 days
  (max 6 cycles)
  CR+PR: 47.8%
WM1 progression-free survival

Factors influencing PFS
Negatively: Chlorambucil, albumin<35g/l, plt<100, age>70y

<table>
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<tr>
<th>Treatment</th>
<th>N</th>
<th>Median (months)</th>
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<tr>
<td>Fludarabine</td>
<td>207</td>
<td>36.3</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>207</td>
<td>27.1</td>
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P=0.01
WM1 survival

OS 5-years

- Chlorambucil: 61.4% [52.9;71.3]
- Fludarabine: 70.3% [62.7-78.8]

(p=0.04)

CD20+ tumor cells
Rituximab?

The addition of R to front-line therapy with CHOP in Lymphoplasmacytic lymphoma (including WM)

- A higher response rate
- Longer time to treatment failure

Fludarabine/combinations
FC and FCR good efficacy

- Hematologic toxicities
  Grade 3/4
    Neutropenia
    Thrombocytopenia
- Infections
- Transformation
- MDS/AML

Purin analogues
No indication in younger patients if autologous ASCT is a later alternative
Other less toxic combinations

Dexamethasone + rituximab + cyclophosphamide (DRC)$^1$

Cyclophosphamide+prednisone+rituximab (CP-R)$^2$

Bendamustine + rituximab$^3$

DRC regimen (n=72)

- CR = 7%
- PR = 67% **ORR = 83%**
- MR = 9%
- SD = 8%
- PD = 8%

Dexamethasone 20 mg IV day 1
Rituximab 375 mg/m2 IV day 1
Cyclophosphamide 100 mg/m2 PO BID days 1–5
courses repeated every 21 days X6

Median time to 50% IgM reduction: 4.1 mo (range 0.7–14)
IgM flare: 32% (>25% IgM increase in 11% of patients)

R-Benda vs R-CHOP: Progression free survival

- Follicular lymphoma:
  - Median (IQR; months): B-R (Not reached, 22.1 to not yet reached), R-CHOP 40.9 (15.2 to not yet reached)
  - HR: 0.61 (95% CI 0.42-0.87), p=0.0072

- Mantle-cell lymphoma:
  - Median (IQR; months): B-R 35.4 (28.8-54.9), R-CHOP 22.1 (15.1-33.8)
  - HR: 0.49 (95% CI 0.28-0.79), p=0.0044

- Marginal-zone lymphoma:
  - Median (IQR; months): B-R 37.2 (31.2-51.2), R-CHOP 28.1 (17.8-51.0)
  - HR: 0.70 (95% CI 0.34-1.43), p=0.3249

- Waldenstrom’s macroglobulinaemia:
  - Median (IQR; months): B-R 69.5 (36.6-73.0), R-CHOP 28.1 (17.8-51.0)
  - HR: 0.33 (95% CI 0.11-0.64), p=0.0033

Other drugs for use in WM

- **Proteosome inhibitors** = bortezomib, carfilzomib
- **Everolimus** → decrease in serum IgM level, but increase in BM involvement
- **Lenalidomide** → unclear anemia
- **Combination**: Carfilzomib, Rituximab and Dexamethasone (CaRD)
  Highly active neuropathy-sparing approach for proteasome-inhibitor based therapy in WM

Bortezomib including protocol (BDR)

Cycle 1 (21-days): bortezomib 1.3 mg/m² iv on days 1, 4, 8, 11

Cycles 2-5 (35-days): bortezomib 1.6 mg/m² iv d 1, 8, 15, 22

Rituximab 375 mg/m² 1, 8, 15, 22  (8 infusions R) + Dexa 40 days

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<thead>
<tr>
<th>Reference</th>
<th>CR</th>
<th>PR</th>
<th>MR</th>
<th>SD</th>
<th>PD</th>
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<td>Dimopoulos et al. *</td>
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<td>11%</td>
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<td>Blood. 2013 7;122: 3276-82</td>
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* PFS: 42 months

Peripheral neuropathy in 46% (grade ≥3 in 7%) 8% discontinued bortezomib due to neuropathy
WM therapy today

Low IgM and cytopenias

High IgM → risk of "flare"

Plasmapheresis

Old age and slow progression

Single-agent rituximab

DRC+ Bortezomib

subcutaneously

Single-agent chlorambucil
European trial: European Consortium (ECWM)

DRC versus DRC + bortezomib sc
• **MYD 88 L265P** - trigger NFκB signaling by direct interaction with BTK in WM cells

• **Trial**: Ibrutinib 420mg/dag for 2 years, or until progress/toxicity

• **Mutations** MYD88 L265P in 49/43 (93%)  
  WHIM-like CXCR4 in 10/40 (25%)

Treon et al, ASH 2013, abstract 251
Ibrutinib in relapsed/refractory WM

Response impacted by mutations in CXCR4 but not in MYD88

Major response rate:
- 77% for patients with wild-type CXCR4 vs
- 30% in those with WHIM-like CXCR4 mutations (p=0.018)

Treon et al ASH 2013, abstract 251
PI3K inhibitors

- GS1101/idelalisib* inhibits PI3K-delta
- Copanolib inhibits PI3K-alpha+delta

* a role in lymphocyte activation and mast cell degranulation
PI3K inhibitor idelalisib (Zydelig)

Phase 2 - trial

Indolent B-Cell Lymphoma

• Refractory to rituximab and alkylating agent

• 125 enrolled patients: 58% FL, 22% SLL, 12% MZL, only 8% LPL/WM

Gopal AK, et al ASH 2013, abstract 85
Response with PI3K-delta inhibitor Idelalisib

- Good response in LPL/WM - ORR: 80%
- ORR: 57% ORR consistent across all subgroups, regardless of number of prior regimens, refractoriness to bendamustine or tumor bulk
- Short median FU 9.4 months

Gopal AK, et al ASH 2013, abstract 85
Ongoing trials for relapsed* WM

Randomized, placebo-controlled Phase 3 trial
Indolent lymphomas, including WM and LPL

- Idelalisib in combination with
  - Bendamustine + rituximab (BR) (Gilead study 125)
  - or
  - Rituximab (Gilead study 124)

*Patients without indication for high-dose chemotherapy/SCT
Response evaluation in WM is not easy.

Delayed response

![Graph showing reduction of the monoclonal component during follow-up.](image)
Modern response criterias

Allele specific PCR for MYD88 L265p in CD19+ selected blood cells?

**NO:** Quicker and greater reduction of tumor-cells in blood than in BM, why BM is required
1936 Jens Bing and Axel Neel reported the association hyperglobulinemia and CNS symptoms
• Paresthesia, headache, gait problems, paralysis

Brain infiltration: plasmacells and lymphocytes

Today:
1) Lymphoplasmacytic/-oid cells infiltrating the CNS

2) Non-cellular form: IgM deposition
Bing Neel syndrome

- Infiltration of WM cells in the central nervous system

Meninges (dura & arachnoid)

Intracerebral tumour

Cerebrospinal fluid

Eye Involved?

Spinal Cord
CNS penetrating chemotherapy

Methotrexate
- $\geq 3 \text{ g/m}^2$

Cytarabine
- Intermediate to high dosing $\geq 2 \text{ g/m}^2$

High dose intensive regimens as used in CNS DLBCL

Purine analogues
- Fludarabine
- Cladribine
- Pass blood brain barrier
- Neurotoxicity is dose related
- 6 case-reports described
Diagnosis and workup of the patient with Ig M monoconal gammopathy and amyloidosis

Giampaolo Merlini from the Italian group

AL amyloidosis associated with IgM monoclonal protein: a distinct clinical entity
6% of AL amyloidosis
Impact of bortezomib based regimen on OS

Treatment and outcome of 263 patients with IgM-related AL amyloidosis

Given the rapid activity in patients with non-IgM AL amyloidosis and in WM, bortezomib-based therapy could be used in carefully selected patients

Dimopoulos et al, Blood. 2014 Jul 15

Summary: Waldenström`s macroglobulinemia

- Rituximab-based combinations
- Bortezomib for fast decrease of IgM
- New drugs
  - Inhibitors of the proteasome, BTK, PI3K and Bcl-2
  - MAbs: PD-1, CD38, SLAMF-7

- Risk-benefit
  - “Risk-adapted” therapy, using ISSWM and CXCR4
- Biology: MYD88 and CXCR4-mutations
  - Microenvironment
Thanks to all colleagues in the Swedish group for National guidelines for WM

- Lena Brandefors
- Magnus Svensson
- Monica Sender
- Elena Holm
- Lotfi Kourosh
- Magnus Björkholm
- Elin Helgadottir
- Sigurdur Kristinsson, Island

Thanks to Chara, who will speak about transplantation

Thank You all colleagues in the International Workshops on WM