DIAGNOSIS AND TREATMENT OF WALDENSTRÖM’S MACROGLOBULINAEMIA IN THE NETHERLANDS

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Organisation of hematological care in the Netherlands

- Intensive chemotherapy, including acute leukemia and stem cell transplantation in academic & large hospitals
- Low care/out-patient based chemotherapy, like for indolent lymphoma, chronic leukemia and elderly myeloma, in smaller hospitals with 1 hematologist
- 75-100 new patients each year, seen in 106 hospitals: max 1 new patient per year.

How to create optimal care for very rare disease with wide clinical spectrum like WM?
Team up!

A survey on diagnostic methods and treatment strategies used in patients with Waldenström’s macroglobulinaemia in the Netherlands

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Guideline for diagnosis and treatment of Waldenström’s macroglobulinaemia

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On behalf of the HOVON Multiple Myeloma Working Party and the HOVON Lymphoma Working Party
Survey

• Send out to 261 hematologists, 24 questions in total
• 32% returned

Diagnostic tests available:
100%; serum electrophoresis, CT scan, pathology lab
> 90%; cold agglutinins, cryoglobulins
< 10%; viscosity measurement, anti-MAG antibody titer test

For diagnosing and staging a combination of tests is necessary
→ on average 7 diagnostic methods (range 2-9)
Multiple answers were possible

- anemia
- symptoms of hyperviscosity
- occurrence of B symptoms
  - night sweats
  - fever
  - weight loss

- a specific level of M-protein
  - median M-protein level of 30 g/L (range 20 - >60 g/L)
IgM flare & Rituximab: what to do?

A. 30%: no problem, no preventive measures
B. 31%: no rituximab in the first treatment cycle
C. 39%: it depends on IgM/complaints:
sometimes plasmapheresis before start of treatment
or no rituximab in the first treatment cycle

C answers: At what level of IgM?
• The mean reported level was 40 g/L with a range from 20 g/L up
to >90 g/L
What would you give?

**Preferred first and second line treatment options**

- **First line treatment**
  - R+ AA = Rituximab with alkylator (chlorambucil)
  - R-COP = Rituximab with cyclophosphamide, vincristin, prednison
  - DRC = Dexamethason, Rituximab, cyclophosphamide
  - Bor = Bortezomib
  - Ben = Bendamustin
  - Tha = Thalidomide
  - AST = Stem cell transplantation

- **Second line treatment**
  - R+PA = Rituximab with purine analogues
What did you give?

First line

<table>
<thead>
<tr>
<th></th>
<th>Would give</th>
<th>Did give</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-COP</td>
<td>36%</td>
<td>33%</td>
</tr>
<tr>
<td>Chloorambucil</td>
<td>14%</td>
<td>30%</td>
</tr>
<tr>
<td>Rituximab-chemotherapy</td>
<td>82%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Second line

- rituximab in combination with purine analogs (55.4%)
- others were R-COP and Bendamustin (~ 20%)
Conclusion survey treatment

- Chloorambucil monotherapy is still frequently used
- R-COP mostly given first line
- R-fludarabin in second line
- No common use of maintenance therapy
- Seldom new drugs are used, sometimes bendamustin
  - No approval - no payment for costs of drugs in hospital
Dutch Guidelines

Diagnostic work up
Classification
Treatment
<table>
<thead>
<tr>
<th></th>
<th>IgM MGUS</th>
<th>Asymptomatic WM</th>
<th>Symptomatic WM</th>
<th>IgM related disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IgM M-protein</strong></td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Bone marrow infiltration</strong></td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>WM related signs or symptoms</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Approach</strong></td>
<td>Follow up (infrequently)</td>
<td>Wait and see</td>
<td>Start treatment</td>
<td>Depending on specific manifestation</td>
</tr>
</tbody>
</table>
Treatment

Hyperviscosity: immediate plasmapheresis + treatment with fast acting regimen: fludarabin, bortezomib
• IgM > 40 g/L: consider preventive measures when starting Rituximab containing treatment

First line:
• Rituximab combination with chemotherapy
• Rituximab monotherapy: IgM related disease
Salvage

• Same regimen, other from first line group
• R-Bendamustine: re-imbursed if progression during or within 6 months after rituximab (containing) therapy

• Newly diagnosed response rate 86%

Progression free survival of 41 patients

Rummel et al, Lancet 2013
Treatment, salvage

- R-bortezomib combination
- No IMIDS; thalidomide, lenalidomide
- Autologous stem cell transplantation
- Maintenance therapy after second line can be considered
Clinical studies

**EMN -06 phase III multicenter, open label randomised study**

"Efficacy of first line Dexamethasone, Rituximab and Cyclophosphamide (DRC) +/- Bortezomib for patients with Waldenstrom Macroglobulinemia"

- 380 patients, Number of study centres; Approximately 150
- **Involved study groups:**
  - FIL (Italian Intergroup), GOELAMS/FCGCLLWM group, GLSG, HOVON Nordic L. Group, Greek Study Group, Spanish Study Group, BNLI (Roger Owen, UK)

**Relapsed patients: in preparation**
Thank you for your attention!