Use of plasma cell immunophenotype as prognostic markers in patients with systemic AL amyloidosis

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• Amyloidosis is a disorder of protein misfolding
• AL amyloidosis
  – Associated with underlying B cell clonal disorder, mainly plasma cell dyscrasias
  – >60% of patients seen at NAC
  – Median OS 2.2 years
• Prognosis driven by advanced organ dysfunction

• Measurement of cardiac biomarkers at presentation is vital

• *Dispenzieri et al. 2004 – Mayo staging*
  
  – Troponin T <0.035 mcg/L
  – NT-proBNP <332 pg/mL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence</th>
<th>Median survival (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>33%</td>
<td>26.4</td>
</tr>
<tr>
<td>II</td>
<td>30%</td>
<td>10.5</td>
</tr>
<tr>
<td>III</td>
<td>37%</td>
<td>3.5</td>
</tr>
</tbody>
</table>
• Prognosis driven by advanced organ dysfunction
• Measurement of cardiac biomarkers at presentation is vital
• *Dispenzieri et al. 2004*
  – Troponin T <0.035 mcg/L
  – NT-proBNP <332 pg/mL
• *Kumar et al. 2012 – Revised staging system*
  – FLC-diff 18 mg/dL
  – cTnT 0.025 ng/mL
  – NT-ProBNP 1,800 pg/mL

<table>
<thead>
<tr>
<th>Stage</th>
<th>Incidence</th>
<th>Median survival (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25%</td>
<td>94.1</td>
</tr>
<tr>
<td>2</td>
<td>27%</td>
<td>40.3</td>
</tr>
<tr>
<td>3</td>
<td>25%</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>23%</td>
<td>5.8</td>
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</table>
Prognosis driven by advanced organ dysfunction
Measurement of cardiac biomarkers at presentation is vital

**Dispenzieri et al. 2004**
- Troponin T <0.035 mcg/L
- NT-proBNP <332 pg/mL

**Kumar et al. 2012**
- FLC-diff 18 mg/dL
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**Dispenzieri et al. 2013**
- ‘Patients with AL amyloidosis who have more than 10% BMPCs have a poor prognosis, similar to that of patients with AL-CRAB...’
• Contribution of underlying PC clone to prognosis unknown

• Paiva et al. 2011
  – Quantification of bone marrow plasma cells (BMPCs) by MFC immunophenotyping is a significant prognostic factor for overall survival
    
    – >5% normal PCs at diagnosis prolonged OS (2-year rates of 88% vs 37%, P .01)
Aim and Methods

• **Aim**
  – Understand the plasma cell phenotype in AL amyloidosis
  – Study the role of plasma cell phenotype on refining prognostic assessment in patients with AL amyloidosis

• **Method**
  – Prospective bone marrow study on newly diagnosed systemic AL amyloidosis patients
  – 8 colour multiparameter flow cytometry
  – Markers tested - CD138, CD38, CD56, CD117, CD28, CD20, CD27, CD19, CD81 and kappa and lambda light chains
Analysis

• Disease assessment
  – Organ involvement by consensus criteria (2010)
  – Organ involvement on SAP scintigraphy

• Outcome assessment
  – Overall survival
  – Haematological response to first line treatment

• In the context of PC phenotype
• 51 consecutive patients

• Median follow up 8.5 months (0.7-24.8 months)

• Aberrant plasma cells:
  – CD38+ CD138+ CD19-
## Patient characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median (range)</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>63.9 (38.5-83.3)</td>
<td></td>
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<table>
<thead>
<tr>
<th>Sex (Male: Female ratio)</th>
<th>2.4:1</th>
</tr>
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<table>
<thead>
<tr>
<th>Monoclonal type</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>15 (29)</td>
</tr>
<tr>
<td>IgA</td>
<td>3 (6)</td>
</tr>
<tr>
<td>IgM</td>
<td>1 (2)</td>
</tr>
<tr>
<td>IgD</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Light chain</td>
<td>31 (61)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Kappa</th>
<th>Median (range)</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>609 (41-4040)</td>
<td>13 (25)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Lambda</th>
<th>Median (range)</th>
<th>No of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>199 (46-2527)</td>
<td>38 (75)</td>
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</table>

### Mayo stage

<table>
<thead>
<tr>
<th>Mayo stage</th>
<th>No of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>9 (18)</td>
</tr>
<tr>
<td>2</td>
<td>17 (33)</td>
</tr>
<tr>
<td>3</td>
<td>25 (49)</td>
</tr>
</tbody>
</table>

![Bar chart showing distribution of Mayo stage](chart.png)
Phenotypes of aberrant PCs

CD 27  CD 28  CD 20  CD 56  CD 81  CD 117
• Expression of CD56 appeared to correlate with both cardiac involvement and dFLC >180mg/L
(spearman’s correlation coefficient, 0.340, p=0.018 and 0.342, p=0.018 respectively)
• There was no correlation between CD27 expression and NT-proBNP or dFLC

Spearman correlation: 0.128, p=0.381 and 0.054, p=0.714
Treatment and response

- NFT
- Thalidomide combination
- Bortezomib combination
- ASCT
- PAD
Treatment and response

- NFT
- Thalidomide...
- Bortezomib...
- ASCT
- PAD

ITT: 66
Evaluable: 74

HR: 30, 33
CR: 23, 26
VGPR: 13, 14
PR: 34, 26
NR: 26, 26
Response in the context of PC phenotype

- The lack of CD27 or CD81 expression correlated with a higher rate of VGPR or better response
  (Spearman’s correlation coefficient = 0.300 and 0.409, p=0.060 and p=0.010 respectively)
Survival analysis

- Median overall survival (OS) was not reached (NR)
Significance of normal PCs

- Better survival in the presence of >5% of normal phenotype (CD38+CD138+CD19+) plasma cells
- The 2 year OS in patients with >5% normal plasma cells was 74% vs 45% in those with <5% normal plasma cells

![Graph showing survival rates]

Median OS NR vs 6.0 months
Better survival in the presence of >5% of normal phenotype (CD38+CD138+CD19+) plasma cells

The 2 year OS in patients with >5% normal plasma cells was 74% vs 45% in those with <5% normal plasma cells

Remains significant within high risk group

Median OS NR vs 3.7 months, p= 0.043
• Expression of CD27 had a significantly worse OS
(5.0 months vs NR, p=0.037)
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? Reflecting Haematological response
• Expression of CD27 had a significantly worse OS
  (5.0 months vs NR, p=0.037)

Expression of CD81 had a worse OS

7.0 months vs NR, p=0.069
• Those expressing CD27+CD56+ had an OS of 2.0 months compared to OS NR in the CD27+CD56- group (p=0.001). OS was NR in either CD27-CD56- or CD27-CD56+ patients.
Summary

• >5% of normal phenotype PCs correlated with superior survival

• CD 56 expression appears to correlate with cardiac involvement and high dFLC at presentation

• CD27 and CD81 expression correlated with poor response to treatment

• Better survival rates seen with CD27 and CD81 negative PCs - reflecting response to treatment

• Co-expression of CD27 and CD56 resulted in worse outcome
Limitations

• Small cohort of patients
  – ?selection bias - M>F, 50% Mayo stage 3

• Variation in method of analysis

• Other markers involved but not tested?

• Heterogeneity of AL amyloidosis
Conclusion

- The presence of CD56+CD27+ appears to define a particularly poor prognostic cohort of patients

- Plasma cell immunophenotype may help to refine the current staging of AL amyloidosis and response to treatment

- Further validation in larger studies is vital
Thank you
Acknowledgements

UKMF

Staff at NAC

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