The return of the normal heart: Resolution of Cardiac Amyloidosis after Bone Marrow Transplantation

Wesley Hospital, Brisbane, Australia
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Dr Ben Fitzgerald, Cardiologist
Dr John Bashford, Haematologist
Dr Greg Scalia, Cardiologist

No Disclosures

Wesley Hospital, Brisbane, Australia
University of Queensland
Background

- Amyloidosis and multiple myeloma are diseases resulting in extracellular deposition of insoluble fibrillar amyloid protein in tissue and organs.
Background

• Amyloidosis and multiple myeloma are plasma cell dyscrasias

• The plasma cell produces the abnormal light chains, which in turn produce the amyloid protein

• This protein is different in each patient, and the properties of the protein determine the tissue and clinical response

Kyle RA. Br J Haematol. 2001  
Adam D et al. Hematology. 2010
Background

• Untreated median survival has been documented at 12 months

• With the development of cardiac involvement, the survival drops to 5 months

• Standard chemotherapy has no impact on survival
Normal Pericardial Fluid LV Echocardiogram – Severe cardiac amyloid 25mm/h
Background

- High dose chemotherapy and bone marrow transplantation (BMT) have been shown to dramatically improve survival in patients with myeloma and amyloidosis
- Haematologic remission has been documented
- Our group has observed unexpected resolution of cardiac amyloidosis in some patients

Kyle RA. Br J Haematol. 2001
Gertz MA, et al, Bone Marrow Transplant. 2000
Methods

• Data collected included:
  – Patient survival
  – The time to normalization in cardiac function from the date of the BMT
  – Ejection fraction
  – Interventricular wall and posterior wall thickness
  – Degree of diastolic dysfunction
  – Left atrial size

• Patients with normalization had the echocardiographic measurements recorded again for comparison
Methods

• Retrospective database analyses were conducted
• 269 patients had high dose melphalan and BMT for amyloidosis or myeloma
• 36/269 (13%) had primary amyloidosis & 233/269 (87%) had multiple myeloma
• 30/269 (11.2%) were identified as having cardiac amyloidosis by ECG and echocardiographic criteria
• 18/30 (60%) with cardiac amyloidosis had primary amyloidosis
Results

- **RESPONDERS:**
  - 15/30 patients had normalization of cardiac function and structure
  - 7/15 responders had primary amyloidosis

- **NON-RESPONDERS**
  - 15/30 patients had no resolution of their cardiac infiltration
  - 11/15 non-responders had primary amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Responders (n=15)</th>
<th>Non-responders (n=15)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>59 years</td>
<td>62 years</td>
<td>p=0.28</td>
</tr>
<tr>
<td>IVS</td>
<td>15.0mm</td>
<td>17.0mm</td>
<td>p=0.26</td>
</tr>
<tr>
<td>PW</td>
<td>14.0mm</td>
<td>14.4mm</td>
<td>p=0.80</td>
</tr>
<tr>
<td>Diastolic function grade</td>
<td>2</td>
<td>2</td>
<td>p=ns</td>
</tr>
<tr>
<td>LAA</td>
<td>25.7 cm²</td>
<td>28.1 cm²</td>
<td>p=0.29</td>
</tr>
<tr>
<td>Survival</td>
<td>71 months</td>
<td>49 months</td>
<td>p=0.0025</td>
</tr>
</tbody>
</table>
Results

- Mean EF for all patients: 58%

- Responders vs. Non-responders

<table>
<thead>
<tr>
<th>Responders</th>
<th>Non-responders</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>60%</td>
<td>0.511</td>
</tr>
</tbody>
</table>

- Responders

<table>
<thead>
<tr>
<th>Pre – BMT</th>
<th>Post – BMT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>61%</td>
<td>0.139</td>
</tr>
</tbody>
</table>
Results: Response to therapy

IVS wall thickness (mm)

Non-responders

Pre: 17±3.6mm
Post: 17±3.7mm

Responders

Pre: 15±2.5mm
Post: 11±1.3mm

www.heartcarepartners.com.au
Results: Responders (n=15)

- Average time to normalization was 25 months (range 4-63 months)
- Only 2/15 have died with prolonged survival (average 71 months) in 13 patients (83.3%)
### Results: Responders (n=15)

<table>
<thead>
<tr>
<th></th>
<th>Pre BMT</th>
<th>Post BMT</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interventricular septum (IVS)</strong></td>
<td>15.0mm</td>
<td>10.7mm</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Posterior wall (PW)</strong></td>
<td>14.0mm</td>
<td>9.8mm</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Diastolic function grade</strong></td>
<td>2</td>
<td>0 - 1</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td><strong>Left Atrial Area (LAA)</strong></td>
<td>25.7 cm²</td>
<td>20.3 cm²</td>
<td>p&lt;0.003</td>
</tr>
</tbody>
</table>
Results: Responders - Diastolic function

- Pre BMT:
  - E:E' = 28

- Post BMT:
  - E:E' = 11
Results: Non-responders (n=15)

- 11/15 died by 13 years of follow-up
- Average survival in non-responders was 49 months from BMT
- No other factor predicted poor outcome
  - (e.g. age, sex, echocardiographic parameters, etc)
Results: Survival

• Normalization of cardiac structure and function was highly predictive of survival
  – Relative risk 0.18
    • (Fisher’s exact test p = 0.0025)

Survival (months)
- Non-responders
- Responders

P = 0.0025

Pre

Post

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GenesisCare
Summary

• These data suggest that patients with cardiac amyloidosis who have prolonged survival will have regression of cardiac infiltration after high dose melphalan and BMT

• On average this cardiac normalization takes just over 2 years from the time of BMT

• This suggests that the process that causes the laying down of intracardiac amyloid protein can be reversed

• Failure to achieve cardiac normalization suggests a poor outcome
Conclusion

• High dose chemotherapy and bone marrow transplantation therapy has been the single most significant advance in the management of plasma cell dyscrasias (amyloidosis and myeloma)
• These data show that many patients with cardiac involvement also have normalization of heart structure and function
• Normalization of cardiac structure and function is highly predictive of survival
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Special thanks to Dr Jeff Presneill, for statistical support
## Results: Non-responders (n=15)

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<tbody>
<tr>
<td>IVS</td>
<td>17.0mm</td>
<td>17.0</td>
<td>0.241</td>
</tr>
<tr>
<td>PW</td>
<td>14.4mm</td>
<td>15.0</td>
<td>0.487</td>
</tr>
<tr>
<td>DD</td>
<td>Grade 2</td>
<td>Grade 2</td>
<td>ns</td>
</tr>
<tr>
<td>LAA</td>
<td>28.5cm²</td>
<td>27.8cm²</td>
<td>0.64</td>
</tr>
</tbody>
</table>
Limitations

- Retrospective observational study
- Echo diagnosis for cardiac amyloidosis rather than by biopsy
- Lack of blinding – possibility for measurement bias
- Single-centre experience
- Small numbers