AL AMYLOIDOSIS: AN UPDATE

Simrit Parmar, MD
COMY, BANGKOK
Amyloidosis and Amyloid Fibrils

Disorder of protein folding

Structurally diverse precursors adopt an abnormal common fibrillar conformation

New properties:
• Bind Congo red and SAP
• Unusual stability

Damage tissue structure, organ function
Progressive and fatal without treatment

Images courtesy Dr Hugh Goodman
In AL amyloidosis, plasma cells in the bone marrow produce too many "free light chain" antibodies. These proteins misfold into amyloid, accumulate in the blood, and deposit in many organ systems.
AL Amyloidosis – when to suspect it?

- Nephrotic range proteinuria
- Cardiac failure with left ventricular hypertrophy in the absence of hypertension or aortic valve disease
- Sensorimotor peripheral neuropathy without obvious cause
- Hepatomegaly with a normal appearance on ultrasound or CT imaging
- Autonomic neuropathy
Making the diagnosis of AL Amyloidosis

• Needs (usually) a tissue biopsy
• Congo Red remains the gold standard
  – Congo Red positivity
  – birefringence and dichroism effects when examined under polarised light microscopy
• Can biopsy:
  – Clinically involved organ
  – Distant site (fat pad, marrow, rectum, salivary glands)
• Accurate subtyping of amyloid is essential
  – Paraprotein + amyloid = highly suspicious of AL ≠ diagnostic of AL
Evaluation of newly diagnosed AL amyloidosis

Define the plasma cell clone

Other investigations

- Assess for symptomatic myeloma
- Assess organ involvement
  - Serum protein electrophoresis + immunofixation
  - Bone imaging
  - Hypercalcaemia
  - Cardiac (ECG, echocardiogram, BNP, troponin, NT-ProBNP)
  - Kidneys (24 hour proteinuria, creatinine)
  - Liver (liver span, ALP)
  - Neuropathy (clinical assessment)
  - Coagulopathy (coagulation profile +/- FX level)
  - Cardiac MRI
  - 24 hour Holter monitor
  - Nerve conduction studies
  - Upper endoscopy + colonoscopy (+ biopsy)
  - Respiratory function testing
  - CT chest
# Cardiac Staging System

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin</td>
<td></td>
</tr>
<tr>
<td>TnT</td>
<td>&lt;0.035μg/L</td>
</tr>
<tr>
<td>TnI</td>
<td>&lt;0.1 μg/L</td>
</tr>
<tr>
<td>hs-TnT</td>
<td>&lt;77ng/L</td>
</tr>
<tr>
<td>Brain Natriuretic Peptide</td>
<td></td>
</tr>
<tr>
<td>NT-ProBNP</td>
<td>&lt;332ng/L</td>
</tr>
<tr>
<td>BNP</td>
<td>&lt;100ng/L</td>
</tr>
</tbody>
</table>

Dispenzieri A et al. JCO 2004
Median OS of Stage III Cardiac AL: 7 months (Wechalekar A et al. Blood 2013)
Cardiac Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Both troponin and BNP below threshold</td>
</tr>
<tr>
<td>Stage II</td>
<td>Either troponin or BNP above threshold</td>
</tr>
<tr>
<td>Stage III</td>
<td>Both troponin and BNP above threshold</td>
</tr>
</tbody>
</table>

Transplant patients

All patients

Revised Cardiac Staging System

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLC diff ≥ 18</td>
<td>1</td>
</tr>
<tr>
<td>cTnT &gt; 0.025</td>
<td>1</td>
</tr>
<tr>
<td>NT-ProBNP &gt; 1800 pg/ml</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage</th>
<th>Score</th>
<th>Median OS (Months)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>94.1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>40.3</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>5.8</td>
</tr>
</tbody>
</table>

Kumar S et al. JCO 2012
Monitoring AL Amyloidosis
## Updated Haematologic Response Criteria

<table>
<thead>
<tr>
<th>Haematologic criteria</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>CR</td>
<td>Negative SPEP/IFE</td>
</tr>
<tr>
<td></td>
<td>Negative UPEP/IFE</td>
</tr>
<tr>
<td></td>
<td>Normal FLC ratio</td>
</tr>
<tr>
<td>VGPR</td>
<td>dFLC &lt; 40mg/L (\text{or } 90% \text{ reduction})</td>
</tr>
<tr>
<td>PR</td>
<td>dFLC decrease ≥ 50%</td>
</tr>
<tr>
<td>NR</td>
<td>Less than PR</td>
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</tbody>
</table>
# Updated Organ Response Criteria

<table>
<thead>
<tr>
<th>Organ</th>
<th>Response</th>
<th>Progression</th>
</tr>
</thead>
</table>
| Heart | NT-proBNP response  
  • >30% and >300ng/L decrease  
  NYHA class response ≥2 class improvement | NT-proBNP increase  
  >30% and >300ng/L  
  Tn increase ≥ 33%  
  EF deterioration ≥ 10% |
| Kidney | 50% decrease in 24hr proteinuria  
  Creatinine must not worsen by 25% over baseline | 50% increase in 24hr proteinuria  
  25% worsening of creatinine |
| Liver | 50% decrease ALP  
  2cm decrease in hepatomegaly | 50% increase ALP |
| PNS | EMG documented improvement | EMG documented deterioration |
OS: 6 Mos NT-ProBNP Response

A

Survival (proportion)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- NT-proBNP progression (at least 300 ng/L and 30% increase; n = 169)
- NT-proBNP stable (n = 108)
- NT-proBNP response (at least 300 ng/L and 30% decrease; n = 100)

P < .001 for all comparisons.
Treatment in AL Amyloidosis
Principles of Treatment

- Reduce monoclonal protein production as profoundly and as quickly as possible
  - Aim for CR or VGPR
  - If this is not possible, PR with organ response

- Tailor therapy to the individual patient
  - Anticipate toxicities of various agents
  - Extent and degree of organ involvement
  - Drug availability

- Organ-specific supportive care
Treatment Approach to Cardiac Amyloidosis

• Early Diagnosis: NT-ProBNP; FLC κ/λ ratio

• Synergize Treatment and Improve Tolerability

• Accelerate Recovery of Cardiac Function

• Supporting Cardiac Function

Pallidini, Haematologica, 2014
What do we know about treatment outcomes in AL amyloidosis?

<table>
<thead>
<tr>
<th></th>
<th>ASCT</th>
<th>MDex</th>
<th>Bortezomib-based chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>20-40%</td>
<td>33%</td>
<td>30-60%</td>
</tr>
<tr>
<td>CR+PR</td>
<td>30-75%</td>
<td>67%</td>
<td>70-100%</td>
</tr>
<tr>
<td>Organ response</td>
<td>40-50%</td>
<td>48%</td>
<td>30-60%</td>
</tr>
<tr>
<td>Median survival</td>
<td>4-6 yrs</td>
<td>5.1 yrs</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Treatment Outcomes in Cardiac Amyloidosis Stage III: European Collaborative Study

- 346 patients
- 42% dead before first response evaluation
- Hematologic response: 33%
- Median OS: 7 months
- Predictors of short OS:
  - NT-ProBNP > 8500
  - SBP < 100
  - Wechalekar A et al. Blood 2013
(A) OS of the whole cohort.

Front-line treatment of AL pts with advanced cardiac involvement

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimens and dosing schedule</th>
<th>N.</th>
<th>Cardiac biomarkers / staging</th>
<th>NYHA class III or IV</th>
<th>HR/CR</th>
<th>CaR</th>
<th>Day 100 mortality</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebovic, et al.</td>
<td>M Dex M 0.11-0.22 mg/Kg on Days 1-4 Dex 20 mg/m² on Days 1-4</td>
<td>40</td>
<td>Median cTnl 0.12 ng/mL</td>
<td>85% class II or higher</td>
<td>58% / 13%</td>
<td>-</td>
<td>23%</td>
<td>10.5 months</td>
</tr>
<tr>
<td>Palladini, et al.</td>
<td>MTDex M 0.22 mg/Kg T 100 mg/Day Dex 20 mg on Days 1-4</td>
<td>22</td>
<td>Stage III: 73%</td>
<td>100%</td>
<td>36% / 4%</td>
<td>18%</td>
<td>27%</td>
<td>5.3 months</td>
</tr>
<tr>
<td>Dietrich, et al.</td>
<td>Intravenous M Dex M 16 mg/m² on Day 1 Dex 40 mg on Days 1-4</td>
<td>61</td>
<td>Stage III: 53%</td>
<td>64%</td>
<td>44% / 11%</td>
<td>14%</td>
<td>33% died on treatment</td>
<td>17.5 months</td>
</tr>
<tr>
<td>Wechalekar, et al.</td>
<td>M Dex T combinations B combinations L combinations</td>
<td>154</td>
<td>Stage III: 100%</td>
<td>52%</td>
<td>40% / 15%</td>
<td>12%</td>
<td>30%</td>
<td>7.1 months (in patients with NT-proBNP &gt;8500 ng/L the median OS is 4.6 months)</td>
</tr>
<tr>
<td>Dinner, et al.</td>
<td>MLDex M 0.18 mg/Kg on Days 1-4 L 10 mg on Days 1-21 Dex 40 mg/week</td>
<td>25</td>
<td>Stage III: 36%</td>
<td>20%</td>
<td>58% / 8%</td>
<td>9%</td>
<td>40%</td>
<td>58% at 12 months (1.8 months in stage III)</td>
</tr>
</tbody>
</table>
Lenalidomide, melphalan and dexamethasone in a population of patients with immunoglobulin light chain amyloidosis with high rates of advanced cardiac involvement

Shira Dinner,1 Wesley Witteles,2 Anosheh Afghahi,1 Ronald Witteles,3 Sally Arai,4 Richard Lafayette,5 Stanley L. Schrier,1 and Michaela Liedtke1

- Overall Hematologic Response: 58%
- Organ Response: 8%
- 1-YR OS: 58%
- Toxic, Ineffective
- Did not alter survival outcomes for patients with high risk cardiac disease
High Dose Therapy Improves Survival in Systemic Light Chain Amyloidosis: 14 Year Follow up

Simrit Parmar, MD, Joshua Howell, PharmD, Michael Wang, MD, Mubeen A Khan, Qaiser Bashir, MD, Jatin J Shah, MD, Nina Shah, MD, Uday Popat, MD, Yvonne Dinh, Sergio A Giralt, MD, Richard Champlin, MD, Robert Z. Orlowski, MD, PhD, Muzaffar Qazilbash, MD
Period: January 1998 to March 2012

Confirmed Amyloidosis n=264

Primary Amyloidosis n=147
- HDT N=80
- CT N=67

MM with Amyloidosis n=110
- HDT N=48

Solitary Amyloidoma n=7
- CT N=62

Median follow up 26 months (0-171 months)

Pathology diagnosis review N=2018
## PT CHARACTERISTICS: HDT vs. CT

<table>
<thead>
<tr>
<th></th>
<th>HDT (N=128)</th>
<th>CT (N=129)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at Diagnosis</td>
<td>56 years (35-74)</td>
<td>56 years (34-73)</td>
<td>NS</td>
</tr>
<tr>
<td>Male Sex</td>
<td>82 (64%)</td>
<td>76 (56%)</td>
<td>NS</td>
</tr>
<tr>
<td>Caucasian Race</td>
<td>84 (65%)</td>
<td>102 (76%)</td>
<td>NS</td>
</tr>
<tr>
<td>≥ 2 Organ Involvement</td>
<td>28 (22%)</td>
<td>34 (26%)</td>
<td>NS</td>
</tr>
<tr>
<td>Cardiac Involvement</td>
<td>21 (16%)</td>
<td>32 (25%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kidney Only Involvement</td>
<td>40 (31%)</td>
<td>23 (18%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Lambda Light Chain</td>
<td>68 (53%)</td>
<td>53 (41%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Induction Treatment</td>
<td>111 (87%)</td>
<td>102 (79%)</td>
<td>0.019</td>
</tr>
</tbody>
</table>
Any Cardiac Involvement and ≥ 2 Organ Involvement is associated with poor outcomes in AL Amyloidosis (n=257)

- Cardiac Involvement 6-year OS 31%
- Other Organs 6-year OS 58%
- ≥ 2 Organ Involvement 6-year OS 35%
- < 2 Organ Involvement 6-year OS 55%

p = 0.01
p = 0.04
Multivariate Analysis HDT associated with improved OS in AL Amyloidosis

Non-significant factors:
- Cardiac involvement
- Kidney involvement
- ≥ 2 organ involvement
- Age at Diagnosis

10-year survival

Conventional Therapy: 16%
AutoSCT: 44%

P < 0.0001

Time from Diagnosis in Months

Cum Survival
AL Pts. Alive at 1-year Post-Diagnosis

AutoSCT: 10-yr OS 46%

CT: 10-yr OS 23%

P = 0.01
Cardiac Amyloidosis Pts. Only

P = 0.024

AutoSCT: 4-yr OS 67%

CT: 4-yr OS 38%
<table>
<thead>
<tr>
<th></th>
<th>NRM-100*</th>
<th>NRM-1 yr**</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRM-100*</td>
<td>12.5%</td>
<td>4%</td>
</tr>
<tr>
<td>NRM-1 yr**</td>
<td>7.5%</td>
<td>13%</td>
</tr>
</tbody>
</table>

*Cause of death includes: infection=4, multi-organ failure=1, unknown=1; p=0.019
** cause of death: infection=4, unknown =4, multi-organ failure =1, liver failure =1; p=0.001
HDT in Primary AL after year 2008 associated with improved OS

4-yr OS 88%  
AutoSCT after 2008

P=0.026

4-yr OS 44%  
AutoSCT before 2008

Time from Transplant in months

Cum Survival
Pre-Transplant Treatment leads to improved OS

Induction Treatment
5-yr OS 56%

No Induction Treatment
5-yr OS 19%

≥ PR; 5-year OS 60%

< PR; 5-year OS 42%
Post-Transplant Response leads to improved OS

CR: 10-year OS 63%

OTHER: 10-year OS 24%
P=0.04

≥ VGPR: 10-year OS 40%

OTHER: 10-year OS 27%
P=0.02
Auto-HCT in Cardiac AL Amyloidosis- Mayo Clinic

- 187 patients from 1996-2008
- Median age: 57 years
- 100-day TRM 16%
  - low serum albumin predicted early death on multivariate analyses
- Hematologic Response: 66%
- Cardiac Response: 41%
- Median OS: 66 months
  - reduced-dose melphalan predicted shorter OS on multivariate analysis
    - Madan S et al. Blood 2012
Auto-HCT in Cardiac AL Amyloidosis - Boston University

- 47 patients
- Stage 3 disease: 24 (51%)
- TRM: 4% overall; 8% in cardiac stage 3
- Hematologic CR + VGPR: 59%
- Cardiac response: 53%
- 3-year OS: 88%
  - Girnius S et al. BMT 2013
Auto-HCT in Cardiac AL Amyloidosis - MDACC: Kongtim P et al. ASH 2013

• 27 patients underwent ASCT between Jan 2002 - Dec 2012
• The median age 53 years (range 36-74)
• Median follow up: 41 months (range 6-173)
• Revised Cardiac stage ≥3 : 14 patients (52%)
• Induction chemotherapy: 24 pts (89%)
• Novel chemotherapy agents: 22 pts (81%)
• Four patients (14.8%) received reduced doses melphalan conditioning (140-180 mg/m²)
Auto-HCT in Cardiac AL Amyloidosis - MDACC: Kongtim P et al. ASH 2013

- 1-yr TRM was 3.7%
- At 1-year post SCT
  - Hematologic response: 24 pts (89%) (CR=26% and PR=63%)
  - Cardiac response: 3 patients (11%)
- Median OS from diagnosis: 58 months
- Median OS from SCT: 46 months (95% CI; 36-55)
- CI Hematologic Relapse at 3 year was 38.5% (95%CI: 23.7-62.5).
- Cardiac progression at last follow up was seen in 1 patient (3.7%).
- Negative predictors of OS
  - No induction therapy prior to SCT
  - NT-proBNP more than 5000 pg/ml
Initial Choice of Therapy

• ASCT should be considered in carefully selected patients and performed at experienced centers
  – Consider “rainy day” PBSC collection in potential ASCT candidates prior to extensive alkylator exposure

• Exclusion criteria
  – Age >65 yrs
  – ECOG performance status ≥ 2
  – TnT >0.06μg/L, cTnI >0.1μg/L, BNP >300ng/L or NT-ProBNP>5000
  – GFR <50mls/min
Initial choice of therapy

On the basis of promising Phase II data, bortezomib-based combinations (CVD, MDV, CyBorD) are preferred upfront treatment strategy

Caveats
- No randomised or long-term data
- Funding/access to bortezomib in AL amyloidosis
- Bortezomib-based regimens should be avoided in patients with:
  - Grade 3 peripheral sensory neuropathy
  - Painful neuropathy
  - Significant autonomic neuropathy
## Case control studies

**UK: CVD vs CTD**

<table>
<thead>
<tr>
<th></th>
<th>CVD</th>
<th>CTD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+VGPR</td>
<td>33%</td>
<td>38%</td>
</tr>
</tbody>
</table>

**Italy: BMDex vs MDex**

<table>
<thead>
<tr>
<th></th>
<th>BMDex</th>
<th>MDex</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR+VGPR</td>
<td>39%</td>
<td>25%</td>
</tr>
</tbody>
</table>

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**Figure 1. Overall survival according to treatment type**

- **CVD**
- **CTD**

- **BMDex (33 patients)**
- **MDex (66 patients)**

- \( p = 0.754 \)
A Phase I/II Clinical Trial of PMD in Newly Diagnosed Untreated Systemic AL Amyloidosis

Newly Diagnosed AL Amyloidosis

PMD x 2 Cycles

Transplant Eligible

Harvest Stem Cells

PMD x 2 cycles

ASCT

≥ PR at 3 mos

Transplant Ineligible

PMD x 4 Cycles

≥ PR

Maintenance Therapy with Pomalidomide
RCT of MDex vs BMDex

Systemic AL amyloidosis
- Untreated
- Not eligible for MEL 200 SCT

Stratify as
- Cardiac Stage I or Stage II

Randomize
- MDex
- BMDex

Progression-free Survival at 2 years

Open in:
- Europe
- Australia
First-line treatment (Chemotherapy × 3 cycles¹, or ASCT)

- CR or VGPR
  - Consolidate with further 3 cycles of chemotherapy (non-ASCT patients), then observe²
- PR
  - Organ response
  - No organ response
- <PR
  - Second-line treatment

  - Second-line treatment available and not contraindicated
  - Second-line treatment not available or contraindicated
  - 3 further cycles of chemotherapy, then observe²
  - Second-line treatment
ANNUAL UPDATES ON HEMATOLOGY AND ONCOLOGY

www.aphcon.org/aubho

Bangkok, Thailand
Aug 29-30, 2014