An approach to treatment of AL Amyloidosis

Ashutosh Wechalekar
Senior Lecturer/Consultant Haematologist
UK National Amyloidosis Centre
University College London Medical School
London

AL amyloidosis – a tale of two diseases

Bone marrow

Immunoglobulin (antibody); monoclonal, also known as a paraprotein

Light chains (antibody fragments) may form amyloid
Potential targets for treatment in AL amyloidosis

Aims and Goals of treatment

**AIM:** Reduce the light chains “enough” to allow balance to tip towards breakdown of amyloid protein

**Goal:**
- improve survival
- improve organ function
- improve quality of life

... and do that in a way that doesn’t do more harm than good
What happens if I don’t have treatment?

- With ongoing supply of the raw material - amyloid formation will continue
- Almost all cases will progress and often very rapidly
- Average survival without treatment is less than a year
  - 6 months vs 12 months (Skinner, Am J Med. 1996;100:295)
  - 8.5 months vs 17 months (Kyle, N Engl J Med 1997;336:1202)

Survival in AL amyloidosis – previous decades

Patients diagnosed between 1966 -1988
Survival ~ 13 months

Kyle et al. Blood; 93(3);1999
Drugs used for AL chemotherapy

• “Traditional” Chemotherapy agents
  – Melphalan (Mel)
  – Cyclophosphamide (Cyclo)
  – Doxorubicin (Adriamycin)
  – Vinristine (V)

• “Novel agents”
  – IMiD’s
    • Thalidomide
    • Lenalidomide
  – Proteosome Inhibitors
    • Velcade
    • PR171

• Corticosteroids
  – Dexamethasone (Dex)
  – Prednisone (Pred)
  – Methylprednisone
  1 mg Dex = ~5 mg Pred

Why do we use drug combinations for treatment?

- Mel/Cyclo/Dox
- Dex/Pred
- Thalidomide
- Lenalidomide
What is a response or relapse?

- **Haematological response or FLC response**
  - Reduction in the light chain or paraprotein
    - Partial response (PR) - at least 50% reduction
    - Complete response (CR) - Normal FLC and no detectable paraprotein
    - Very good partial response (VGPR) - >=90% decrease in FLC

- **Amyloid organ response or “regression”**
  - Improvement in amyloidotic organ function – e.g. decrease in protein loss in urine or improvement in liver function tests
  - Decrease in amyloid load in SAP scan

- **Relapse**
  - Rise in FLC on serial measurement or paraprotein or re-appearance of PP

- **Amyloid progression**
  - Worsening of organ function or increase in amyloid load on SAP scans

General side effects of various drugs in AL treatment

**Chemotherapy drugs**

- Decrease in blood counts
- Tiredness
- Nausea
- Hair loss or thinning
- Specific side effects of various drugs:
  - Doxorubicin – can affect heart after prolonged use
  - Melphalan – can damage stem cells
  - Cyclophosphamide – can lead to cystitis and blood in urine in high doses
Side effects of drugs and drug combinations

Fluid retention and tiredness are often the main side effects

Thalidomide
- Tiredness, sleepiness, light headed
- Peripheral neuropathy (nerve damage)
- Thrombosis (blood clots)
- Fluid retention

Lenalidomide
- Low blood counts
- Thrombosis
- Skin rashes
- Neuropathy - rare

Dexamethasone
- Fluid retention
- Mood changes
- High blood sugar

Velcade
- Peripheral neuropathy
- Thrombocytopenia (low platelet count)
- Diarrhoea/constipation
- Low blood pressure
- Fatigue
- Shingles
Why do we assess haematologic or FLC response?

Depth of response linked to outcome

- 0-50% dFLC response (n=83)
- 51-90% dFLC response (n=48)
- >90% dFLC response (n=72)

Survival according to dFLC response - Intention to treat analysis

- Months from diagnosis
- Percent survival

How long will the treatment continue

AIM: Reduce the light chains “enough” to allow balance to tip towards breakdown of amyloid protein

- Until the maximal benefit is achieved – i.e. Complete response or “plateau”
- Usually between – 4-6 cycles
- With M-Dex – longer treatment may be needed
Do ALL patients need to achieve a CR?

- Risks of prolonged chemotherapy
- Needs to be decided on each individual case basis
- SAP scans invaluable to monitor
- Role of biomarkers – NT-ProBNP?

Biomarkers in risk stratification – NT-ProBNP

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alive</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Response</td>
<td>38%</td>
<td>6%</td>
</tr>
<tr>
<td>PR + No BNP resp.</td>
<td>78%</td>
<td>4%</td>
</tr>
<tr>
<td>PR + BNP resp.</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>CR</td>
<td>4%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Pre-treatment
Post-treatment
Treatment options in AL

Current three main drugs for AL treatment
Oral Cyclo-Thal-Dex (CTD)

- >300 patients treated
- Over response 72%
  - CR 23%
- Important to manage toxicity

Wechalekar et al Blood 2007
Gibbs et al ASH 2008

Before CTD
6 mo. after CTD

Toxicity

Lane et al ALChemy study data ASH 2011
Bortezomib in AL amyloidosis

- Overall responses 71%
- Median PFS ~ 2 years

Rapid responses to Velcade in AL
Oral Melphalan dexamethasone

- Well tolerated
- Overall responses 64%
- Median PFS 3.8 yrs
- OS – 5.5yrs
- Stem cell toxic
- Rapidity of response – median time to respond 4 months

Lenalidomide (Revlimid) in AL amyloidosis

Overall hematologic response 16 (67%)
Hematologic CR 7 (29%)
Hematologic PR 9 (38%)

NAC data ( ~90 patients)
Overall hematologic response 57%
VGPR or better 26%
Autologous peripheral blood stem cell transplant

The Autologous Transplant Process
1. Collection
   Stem cells are collected from the patient’s bone marrow or blood.

2. Processing
   Blood or bone marrow is processed in the laboratory to purify and concentrate the stem cells.

3. Cryopreservation
   Blood or bone marrow is frozen to preserve it.

4. Chemotherapy
   High dose chemotherapy and/or radiation therapy is given to the patient.

5. Reinfusion
   Stem cells are thawed and reinfused.

Organ response - 78%
Organ response - 39%

Stem cell transplantation – good long term outcomes

Cibeira et al. Blood; 2011; 118 (16); 4646-52
Chemotherapy vs. Transplantation

FOR
• Better complete clonal responses
• "One shot" treatment
• Longer clonal remission
• Translates to better long-term survival and organ function

AGAINST
• Higher early mortality
• Prolonged hospital admission
• No proof of better outcomes

How do various regimes compare?

[Bar chart showing different outcomes for various regimes]
How do various regimes compare?

WHAT IS NEW?
Cyclo-Vel-Dex – UK experience

- N=37 (Upfront –14; Relapsed 23)
- Stage III – 46%

- Organ response – 46% including cardiac 11%

Venner et al ASH 2011
### Bortezomib-combinations in AL amyloidosis

<table>
<thead>
<tr>
<th>Regime</th>
<th>Zonder et al</th>
<th>Mikhael et al</th>
<th>Venner et al</th>
<th>Palladini et al</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>33</td>
<td>10 (upfront)</td>
<td>20 (upfront)</td>
<td>50 (upfront)</td>
</tr>
<tr>
<td>Regime</td>
<td>V-MDex</td>
<td>C-V-D</td>
<td>C-V-D</td>
<td>V-Mdex – 33 C-V-D - 17</td>
</tr>
<tr>
<td>Hematologic response</td>
<td>94%</td>
<td>93%</td>
<td>95%</td>
<td>Stage I/II – 67% Stage III – 40%</td>
</tr>
<tr>
<td>CR</td>
<td>63%</td>
<td>60%</td>
<td>65%</td>
<td>Stage I/II – 27% Stage III – 5%</td>
</tr>
<tr>
<td>Organ response</td>
<td>62%</td>
<td>40%</td>
<td>46%</td>
<td>NA</td>
</tr>
</tbody>
</table>

Zonder et al. Blood (ASH Annual Meeting Abstracts) 2010  

### Newer proteosome inhibitors

- **MLN9708 (Oral “velcade”)**
  - Phase I trial completed
  - Phase III trial due to start shortly (including NAC, London) – probably December 2012

- **Carfilzomib** – approved for relapsed myeloma in US
  - no neuropathy
  - ?cardiac side effects
## Cyclo-Lenalidomide (Revlimid)-Dex

<table>
<thead>
<tr>
<th></th>
<th>Kastritis et al. abstract 428</th>
<th>Palladini et al. abstract 2863</th>
<th>Kumar et al. abstract 3853</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematologic response</strong></td>
<td>61%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td>0%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Organ response</strong></td>
<td>22%</td>
<td>15%</td>
<td>24%</td>
</tr>
<tr>
<td><strong>Median time to response</strong></td>
<td>2.5 months</td>
<td>1.9 months</td>
<td>N.A.</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>Higher in RF</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td><strong>most common SAE</strong></td>
<td>infection, anemia</td>
<td>neutropenia, fluid retention</td>
<td>cytopения, fatigue</td>
</tr>
</tbody>
</table>

## Lenalidomide-MDex in AL amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Moreau et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematologic response</strong></td>
<td>58%</td>
</tr>
<tr>
<td><strong>Complete remission</strong></td>
<td>42% of those on 15 mg</td>
</tr>
<tr>
<td><strong>Organ response</strong></td>
<td>50%</td>
</tr>
<tr>
<td><strong>SAE</strong></td>
<td>N.A.</td>
</tr>
<tr>
<td><strong>Most common SAE</strong></td>
<td>cytopenia</td>
</tr>
</tbody>
</table>
Pomalidomide in AL amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Dispenzieri et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematologic response</td>
<td>38%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>8 PR and 3 VGPR (no CR)</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>18</td>
</tr>
<tr>
<td>Organ response</td>
<td>3</td>
</tr>
<tr>
<td>SAE (≥ Grade 3)</td>
<td>21</td>
</tr>
</tbody>
</table>

Bendamustine

- Old drug – new use
- Italy - 15 patients
- 55% response rates
  - Mainly PR
- UK – few patients
  - Benda-Thal-Dex
  - CR in 2 patients
Impact of novel treatments on survival in AL

“We can’t stop the ringing in your ear, but we can modify it to your favorite ringtone.”

Bortezomib
Revlimid
Thalidomide

2001-2003 – median 1.7 yr; 4 yr OS: 30%
1996-2000 – median 1.4 yr; 4 yr OS: 20%
Till 1995 – median 1.5 yr; 4 yr OS: 20%

2004-2007 – median 2.2 yr; estimated 4 year OS: 38%
2006-2012 – median not reached; estimated 4 year OS: >30%
**Who gets what?**

- **Rapid response** – Velcade or CTD
- **Fit patient with one organ** - ?ASCT
- **Patients with marked resistant fluid overload**
  - need care with dexamethasone
- **Neuropathy** – avoid thalidomide/Velcade
- **Frail patient** (age, organ damage) - single agent weekly velcade or MPT or M-Dex
- **Personal or physician preference**

**Treatment at relapse**

- **Use an agent not used previously**
- **NICE** (National Instt. For Clinical Excellence) myeloma guidance dictates treatment choice
- **Patients relapsing after 1st line treatment**
  - NICE eligible for VELCADE
- **Patients relapsing after 2 or more previous treatments**
  - NICE eligible for LENALIDOMIDE
### Clinical trials in UK

<table>
<thead>
<tr>
<th>Category</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newly diagnosed patients</strong></td>
<td>Phase III trial of Oral M-Dex vs. Velcade-M-Dex</td>
</tr>
<tr>
<td></td>
<td>REVEAL – study of Vel-Cyclo-Dex vs. Vel-Dex</td>
</tr>
<tr>
<td><strong>Relapsed disease</strong></td>
<td>MLN9708-Dex vs. best other</td>
</tr>
<tr>
<td></td>
<td>A possible pomalidomide trial – details to be finalised</td>
</tr>
</tbody>
</table>