Current treatment strategies for AL amyloidosis

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Underlying clone
Excess production of unstable FLC
Misfolded light chains allowing exposure of hidden epitopes which allow aggregation
Pre-fibrillar aggregates
Amyloid fibril formation in an ordered β-pleated sheet structure in tissues
Organ damage due to fibril deposition
Direct tissue toxicity (mainly affecting the heart)

Potential targets for treatment in AL amyloidosis – a tale of two diseases

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

Drugs used for AL chemotherapy

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

“Novel agents”
- IMIDs
- Thalidomide
- Lenalidomide
- Pomalidomide
- Proteasome inhibitors
- Velcade
- Carfilzomib

Corticosteroids
- Dexamethasone (Dex)
- Prednisone (Pred)
- Methylprednisone
- 3 mg Dex = "Sing Pred"

Why do we use drug combinations for treatment?

Mel/Cyc/Dox
Dex/Pred
Thalidomide
Lenalidomide
Cell death

Aims
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What happens if I don’t have treatment?

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* 6 months vs 12 months (Blumen, Am J Med. 1996;100:132-136)
* 8.5 months vs 17 months (Kyle, N Engl J Med 1997;336:1202)
**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 amyloid organ function - e.g., decrease in protein loss
- Improvement in organ function tests
- Decrease in amyloid load on SAP scan

**Relapse**
- Rise in FLC on repeat measurement or reappearance of PP

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

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**General side effects of various drugs in AL treatment**

**Chemotherapy drugs**
- Decrease in blood counts
- Tiredness
- Nausea
- Hair loss or thinning
- Fluid retention

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**Side effects of drugs and drug combinations**

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

*Dexamethasone*
- Fluid retention
- Mucous changes
- High blood sugar

*Lenalidomide*
- Low blood counts
- Thrombosis
- Skin rashes
- Neutropenia - can

*Velaque*
- Peripheral neuropathy
- Thrombocytopenia (low platelet count)
- Other bone/constipation
- Low blood pressure

*Fluid retention and tiredness are often the main side effects*

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**Why do we assess haematologic or FLC response?**

**Depth of response linked to outcome**

![Graph showing depth of response linked to outcome](image)

- p < 0.0001
- >90% dFLC response (n=72)
- 51-80% dFLC response (n=48)
- 0-50% dFLC response (n=83)

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**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
- Increasing the aim is to get a near CR
Goals of therapy have to be individualised

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

Pre-treatment Post-treatment

Current three main drugs for AL treatment

- Thalidomide
- Velcade (Bortezombi)
- Revlimid (Lenalidomide)

Dexamethasone
Cyclophosphamide
Melphalan

CTD, M-Dex, Vel-Dex, C/M-Vel-Dex, Len-Dex
Bendamustine, Pomalidomide, Carfilzomib, Ixazomib

Bortezomib in AL amyloidosis
- Overall responses 71%
- Median PFS ~ 2 years
- Very rapid responses

Rapid responses to Velcade in AL

Cyclo-Vel-Dex - the current standard of care
- N=230
- Stage III – 49%

Impact of clonal response on overall survival
Oral Cyclo-Thal-Dex (CTD)
- >300 patients treated
- Over response 72%
- CR 23%
- Important to manage toxicity

Before CTD
6 mo. after CTD
Gibbs et al. ASH 2008

Toxicity of treatment (CVD and CTD)
- Grade 3 or greater toxicity – 55% of patients
- Velcade based: 56%*
- Thalidomide base: 63%*
*(p=ns)

Gra d e 3 or greater toxicity –
55% of patients
Velcade based: 56%*
Thalidomide base: 63%*
*(p=ns)

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%)

Proportion surviving
Overall survival (median not reached)
Progression free survival (median 2.5 years)

Oral Melphalan dexamethasone

Lenalidomide – Mdex in AL amyloidosis
- Haematologic response 58%
- Complete remission 42% of those on 15 mg
- Organ response 50%
- SAE N.A.
- Most common SAE cytopenia

Cycle – Lenalidomide (Revlimid) - Dex

<table>
<thead>
<tr>
<th>Study</th>
<th>Kastritis et al. abstract 429</th>
<th>Palladini et al. abstract 2863</th>
<th>Kumar et al. abstract 3853</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematologic response</td>
<td>61%</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>0%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Organ response</td>
<td>22%</td>
<td>15%</td>
<td>24%</td>
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<tr>
<td>Median time to response</td>
<td>2.5 months</td>
<td>1.9 months</td>
<td>N.A.</td>
</tr>
<tr>
<td>SAE</td>
<td>Higher in RF</td>
<td>60%</td>
<td>69%</td>
</tr>
<tr>
<td>Most common SAE</td>
<td>Infection, anemia, neutropenia, fluid retention, cytopenia, fatigue</td>
<td></td>
<td></td>
</tr>
</tbody>
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### Pomalidomide in AL amyloidosis

<table>
<thead>
<tr>
<th></th>
<th>Dispenzieri et al (Low dose)</th>
<th>Palladini et al (higher dose)</th>
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</thead>
<tbody>
<tr>
<td>Haematologic response</td>
<td>38%</td>
<td>67%</td>
</tr>
<tr>
<td>Complete remission</td>
<td>8 PR and 3 VGPR (no CR)</td>
<td>18% VGPR</td>
</tr>
<tr>
<td>Discontinuation</td>
<td>18</td>
<td>18%</td>
</tr>
<tr>
<td>Organ response</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>SAE (≥ Grade 3)</td>
<td>21</td>
<td>67%</td>
</tr>
</tbody>
</table>

### Bendamustine
- Old drug – new use
- 36 patients
- 55% response rates
- Mainly PR
- UK – available via the cancer drugs fund

### Autologous peripheral blood stem cell transplant

**The Autologous Transplant Process**

1. Collection
2. Processing
3. Consolidation
4. Chemotherapy
5. Recovery

### Chemotherapy vs. Transplantation

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

**AGAINST**
- Higher upfront risks
- Prolonged hospital admission
- CR in <50%

### Stem cell transplantation – good long term outcomes

- Organ response – 78%
- Organ response – 39%

### Who should be considered for ASCT
- Age <65(-70) yrs
- Good kidney function
- No significant heart involvement
- Good albumin
- No significant gut bleeding
- Physically (and mentally) fit
- ~ 15% of all patients will be eligible
- Relaxation of some criteria in younger patients <50 yrs, relapsed disease
- Important to consider ASCT in all with marked BM plasma cell infiltration
How do various regimes compare?

What is new?

Newer proteasome 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
- Daratumumab and other antibodies to plasma cells

Ixazomib (MLN9708) Phase I trial

- Dose 4 mg and 5.5 mg
- Total 4/12 responded
- 7/12 had stable disease
- Dose of 4 mg was identified as the safe dose

Phase III trial ongoing at RFH, Oxford, Birmingham, Manchester

Merisi et al ASH abstract 2012

Impact of novel treatments on survival in AL

How can we choose a treatment regime?
**Who gets what?**

- **Most patient** – CVD or less frequently CTD/MDex
- **Fit patient with one organ** – Autologous transplant
- **Patients with marked resistant fluid overload** - need care with dexamethasone
- **Neuropathy** – avoid thalidomide/Velcade
- **Frail patient (age, organ damage)** - single agent weekly velcade or M-Dex
- **Personal or physician preference**

**Treatment at relapse**

- Use an agent not used previously
- **NICE (National Inst. For Health and Clinical Excellence)** myeloma guidelines and Cancer Drugs fund decides treatment choice
- **Patients relapsing after 1st line treatment**
  - NICE guidance for VELCADE
- **Patients relapsing after 2 or more previous treatments**
  - NICE guidance for LRPALDIX
- **Patients previously treated with Vel, Len, cyclo/mael**
  - Pomalidomide or Bortezomib

**Clinical trials in the UK**

- **Newly diagnosed patients**:  
  - Phase III trial of Oral M-Dex vs. Velcade-M-Dex  
  - REVEAL – study of dose escalation in advanced cardiac AL
- **Relapsed disease**:  
  - MLN9708-Dex vs. best other  
  - Car-Thal-Dex trial in set up

**Myeloma UK resources**

- **AL amyloidosis Infoguides**:
  - Cyclophosphamide, Thalidomide and Dexamethasone (CTD)
  - High-Dose Therapy and Stem Cell Transplantation
  - Melphalan and Dexamethasone (Mel-Dex)
  - Revlimid®
  - Velcade®
- **AL amyloidosis Infosheets**:
  - Steroids
  - Serum Free Light Chain Assay
  - The SAP scan

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