Current treatment strategies for AL amyloidosis

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Potential therapeutic avenues in amyloidosis

High flux dialysis
Reduce precursor protein
Treatments to kill plasma cells
Plasma cell clone

SAP
Anti-SAP antibodies
GAG’s
Eprodisate
Doxycycline
EGCG
Oligomers
Mis-folding
Interfere with formation or accelerate removal
Anti-fibril antibodies
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;100:290)
- 8.5 months vs 17 months (Kyle, NEJM 1997;336:1202)
Deeper responses (i.e. Lower light chains) = better outcomes

Impact of the depth of reduction in light chains on outcomes

Treatment options in AL
Drugs used for AL chemotherapy

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

“Novel agents”
- IMiD’s
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- Proteosome Inhibitors
  - Velcade
  - Carfilzomib

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

Why do we use drug combinations for treatment?

Mel/ Cyclo/ Dox

Dex/ Pred

Cell death

Thalidomide
Lenalidomide
**Terms for efficacy of treatment**

**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 paraprotien
  - 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

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

**Chemotherapy drugs**
- Decrease in blood counts
- Tiredness
- Nausea
- Constipation/Diarrhoea
- Fluid retention
### Side effects of drugs and drug combinations

**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

Fluid retention and tiredness are often the main side effects.
How long will the treatment continue

**AIM:** Serum free light chains of <40 mg/L or as near normal as possible is the goal of treatment

- Rate of response
- Percentage of abnormal plasma cells in the bone marrow
- Tolerance to treatment

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**Treatment based on disease severity**

### AL with Low risk disease (15-20%)
- Stage 1/Early stage 2
- Young (<70 yrs)
- Fit
- No or early cardiac involvement
- Good renal function

### AL with intermediate risk disease (~60%)
- Stage 2 and early stage 3
- ECOG 2
- SBP >100 mm Hg
- NT-proBNP <8500 ng/L
- Age ?

### AL with high risk disease (15-20%)
- Arrhythmias
- Severe heart failure
- Low BP
- Bleeding
- Very frail
- Older patients (>75-80 yrs)

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Chemo or Stem cell transplant  
Chemotherapy
Risks of prolonged chemotherapy
Needs to be decided on each individual case basis
SAP scans useful to monitor
Role of biomarkers

Therapy has to be individualised

Pre-treatment  Post-treatment

Current three main drugs for AL treatment

IMiDs (Thal, Len, Pom)
Velcade (Bortezomib)
Alkylators (Cyclo, Melp, Benda)
Steroid (Dexamethasone)

CVD, VMDex, VRD, CTD, Mdex, VMP, etc
Bendamustine, Carfilzomib, Ixazomib, Panabinostat, Daratumab
Bortezomib (Velcade) in AL amyloidosis

- Very rapid and deep responses
- Has transformed outlook for many patients

Is a subcutaneous injection
Given once or twice weekly

Rapid responses to Velcade in AL

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Kastritis E et al. JCO 2010;28:1031-1037
Cyclo-Vel-Dex - the current standard of care

- N=230
- Stage III – 49%


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

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

Lenalidomide (Revlimid) in AL amyloidosis

Used in:
- Patients with neuropathy
- Relapsed after previous velcade
- Patients not responding to velcade

NAC data
Overall hematologic response 57%
VGPR or better 26%

Mahmood et al BHJ 2014
**Lenalidomide combinations**

Combined with Dex in all cases
Improved responses when combined with:
- Cyclophosphamide/Melphalan
- Velcade

<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>cytopenia, fatigue</td>
</tr>
</tbody>
</table>

**Pomalidomide in AL amyloidosis**

Newest agent on the IMiD class
Probably best tolerated
Licensed for patients relapsed after or not responding Velcade and Len

*Pom-Dex or Cyclo-Pom-Dex commonly used combinations*

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

- Old drug – new use
- 36 patients
- 55% response rates
  - Mainly PR
- Not particularly effective on its own
- Works better combined with Thal or Velcade

Palladini and Schoenland et al  ASH Annual Meeting Abstracts 2012

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 reinflused.
Stem cell transplantation – good long term outcomes

Organ response – 78%
Organ response – 39%

FOR
• Only possible in selected case based on fitness and organ involvement
• “One shot” treatment
• Long lasting responses
• Translates to better long term survival and organ function

AGAINST
• Higher upfront risks
• Hospital admission
• CR in <50%
• Limited centers in UK have experience

Increasingly used in UK for:
• Patients with significant bone marrow plasma cell infiltrates
• At relapse
• For poor response to velcade based therapy

Chemotherapy vs. Transplantation

Cibeira et al. Blood; 2011; 118 (16):4646-52
Toxicity – Achillis heel of treatment in AL

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

What is new?
### Newer proteasome inhibitors

- **Ixazomib** (Oral “velcade”)
  - Phase I trial completed
  - Phase III trial ongoing
  - Not available outside of trial

- **Carfilzomib** – approved for relapsed myeloma in US
  - Available in UK via expanded access programme
  - Not free
  - UK trial in AL due to start 2016

- **Panabinostat**
  - Affects DNA function in the cell
  - Available on a compassionate use programme in combination with velcade

### Antibodies to plasma cells

**DARATUMUMAB**

- FDA approves Darzalex for patients with previously treated...
- Today the U.S. Food and Drug Administration granted accelerated approval for Darzalex (daratumumab) to treat patients with multiple myeloma...
- Darzalex (Daratumumab) Approved By FDA For Multiple Myeloma

- Gemma Announces U.S. FDA Approval of DARZALEX...
UK Challenge – access to drugs

I DON’T CARE WHAT IT SAYS ON THE “CHOCOHOLICS” WEBSITE I’M NOT ABLE TO PRESCRIBE CHOCOLATE MINI EGGS ON THE NHS.

Potential therapeutic avenues in amyloidosis

- High flux dialysis
- Treatments to kill plasma cells
- Plasma cell clone
- Reduce precursor protein
- Mis-folding
- Interfere with formation or accelerate removal
- Oligomers
- Amyloid fibrils
- Anti-fibril antibodies
- Eprodisate
- Doxycycline
- EGCG
- Anti-SAP antibodies
- SAP
- GAG’s
## Current clinical trials in AL amyloidosis

### Upfront
- VITAL – NEO001D with CyBorD
- BMDex vs. Mdex (Phase III)
- Radiolabelled CD66 for ASCT conditioning

### Relapsed
- Ixa-Dex vs. Physicians choice
- CATALYST – Car-Thal-Dex
- NEO001D Maintenance

### In planning
- CPHPC+anti-SAP Phase II
- Daratumumab+?Ixa-Dex

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## Significant cardiac AL needs careful treatment

![Survival probability graph](image)

- Stage I
- Stage II
- Stage IIIa
- Stage IIIb

**P<0.001**