Latest advances in AL amyloidosis

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Improved outcomes for newly diagnosed AL amyloidosis over the years 2000-2014: Cracking the glass ceiling of early death

6-month mortality from 37% to 24%.

At present, AL amyloidosis represents the most successful example of effective treatment of all types of amyloidosis

Heart involvement is the determinant of survival

- 30% died at 6 months, 94% of heart failure/sudden death

198 patients with renal and without cardiac involvement

Cardiac involvement
- 750 patients
- Median survival 18 months

Overall population
- 984 patients
- Median survival 40 months

P<0.001
Molecular events leading to AL amyloidosis

Incidence 10.5 per million person-years\(^1\) - 10-15% of multiple myeloma patients develop AL amyloidosis\(^2\)

Small dangerous B cell clone\(^3\)
\(\lambda\) LC in \(~78\%\)

Kinetically/thermodynamically unstable LC\(^4-7\)

The amyloidogenic clone

- Low plasma cell burden (median 10%) and proliferative rate (Gertz et al, *Blood*. 1989)

- Poor prognosis if >10% (AL+MM) (Kourelis et al, *JCO* 2013 – Veelken et al, *ISA* 2018 PC075)

- Clonal PCs in AL have similar phenotypic and CNA profiles as those in MM, but their GEP is similar to that of normal PCs. (Paiva et al, *Blood* 2016)


- 4 SNPs reached genome-wide significant associations in clinical profile-specific AL amyloidosis (Meziane et al, *Haematologica*. 2017)

- AL amyloidosis has a lower complexity mutational pattern than MM (Rossi et al, *Blood Cancer J* 2017)

Is the AL clone more amenable of eradication than MM clone?
Multiparametric flow cytometry in AL amyloidosis

**Patients who achieved ≥ VGPR**

- Improvement in **cardiac response** at 12 months compared to 6 months, an additional 33% patients compared to 15% of patients with residual monotypic cells ($p = 0.003$)

- **Renal response** additional 19% of patients compared to 3% in patients with residual monotypic plasma cells ($p = 0.02$).

Landau et al, *ISA 2018 PC090*

Sidana et al, *Leukemia 2018*
Minimal residual disease by next generation flow cytometry in patients with AL amyloidosis who attain amyloid complete response

Compared to the time of aCR achievement, further renal response was obtained in 9 of 13 evaluable MRD negative patients (69%) and in 2 of 11 MRD positive patients (18%, P=0.034)

Characterization of the amyloidogenic clone

Serum and urine immunofixation and FLC measurement (mass spectrometry)
(Palladini et al, Clin Chem. 2009)

Bone marrow studies

• Poor prognosis if >10% (AL+MM) (Kourelis et al, J Clin Oncol. 2013)

• High frequency of t(11;14) translocation (~40-60% vs 17% in MM): lower benefit from bortezomib and IMiDs than from M-Dex and HDM (Bochtler et al, J Clin Oncol. 2015 - Muchtar et al, Leukemia 2016)

• Gain of 1q21 (~25%): poor outcome with M-Dex (Bochtler et al, Amyloid 2014) overcome by HDM and bortezomib (Bochtler et al J Clin Oncol 2015, Blood 2016)

Bone imaging (low-dose CT, MRI)
Light Chain (AL) amyloidosis: The journey to diagnosis

Survey on 533 patients with AL amyloidosis

Time from initial symptoms to diagnosis

- <6 months: 37.3%
- 6-12 months: 25.7%
- 12-18 months: 9.6%
- 18-24 months: 7.4%
- 2-3 years: 9.6%
- >3 years: 10.5%

Number of physician visits before diagnosis

- 1 visit: 7.6%
- 2 visits: 23.5%
- 3 visits: 20.3%
- 4 visits: 16.8%
- 5 or more visits: 31.8%

Lousada et al, Adv Ther. 2015 and ISA 2018 PA072
McCausland et al, Patient 2017
Lim et al, ISA 2018 PA070
Quock et al, ISA 2018 PA085
Amyloidosis is a great imitator

**Heart**
Heart failure with preserved ejection fraction
Thickened ventricular walls, low voltages at ECG
Dyspnea at rest or exertion, fatigue
Hypotension or syncope
Peripheral edema

**Kidney**
Nephrotic range proteinuria
Renal failure
Peripheral edema

**GI tract**
Malabsorption, weight loss
Bleeding (Factor X def.)

**Nervous system**
**Peripheral:** symmetric lower extremity sensorimotor PN
Carpal tunnel syndrome (bilateral)
**Autonomic:** postural hypotension, erectile dysfunction

→ advanced stage of the disease!
→ need for more sensitive markers of organ involvement

**Liver**
Increased alkaline phosphatase
Hepatomegaly

Periorbital purpura 11%

Macroglossia 14%
Increased serum free light chains precede the presentation of AL amyloidosis by years

Monitor population at risk (MGUS with abnormal $\kappa/\lambda$ ratio) using cardiac (NT-proBNP) and renal (urinary albumin) biomarkers

Weiss et al, J Clin Oncol. 2014

Monitor population at risk (MGUS with abnormal $\kappa/\lambda$ ratio) using cardiac (NT-proBNP) and renal (urinary albumin) biomarkers

Merlini & Palladini, Hematology 2012
Merlini et al, Blood 2013
Palladini et al, ASH 2017 Abstr. 1760

13 patients $\rightarrow$ VGPR/CR + organ response

Palladini et al, ASH 2017 Abstr. 1760
Diagnosis: imaging cardiac amyloidosis

**Echocardiography**
- Strain Doppler imaging
  - Buss et al., JACC 2012

**Cardiac MRI - T1 map - LGE**
- Maceira et al., Circulation 2005
- Banypersad et al., Circ Cardiovasc Img. 2013
- Fontana et al., JACC Cardiovasc Img. 2017

**$^{99m}$Tc-DPD/HMDP/PYP scan**
- AL
- ATTR
  - Rapezzi et al., JACC Img. 2011
  - Gillmore et al., Circulation 2016

**$^{18}$F-florbetapir**
**$^{18}$F-florbetaben**
**$^{11}$C-Pittsburgh compound B**
- Dorbala et al., EJNMMI 2014
- Park et al., Circ Cardiovasc Img. 2015
- Pilebro et al., J Nucl Cardiol. 2017
Diagnostic algorithm for AL amyloidosis
Merlini, Seldin & Gertz, J Clin Oncol. 2011

Diagnosis of amyloidosis relies on Congo red staining of tissue biopsy

Tissue of choice: abdominal fat: innocuous, fast, inexpensive (underutilised):¹
sensitivity 81-84%²,³ + BM biopsy 95% specificity 97%

Biopsy of the labial salivary glands

Biopsy of the organ involved (kidney, heart, nerve, liver)

Typing of amyloidosis is essential for the choice of therapy

Clinical presentation of AL and ATTR amyloidosis overlap

<table>
<thead>
<tr>
<th>Amyloid type</th>
<th>Organ involvement</th>
<th>Heart</th>
<th>Kidney</th>
<th>Liver</th>
<th>PNS</th>
<th>ANS</th>
<th>Soft tissues</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloidosis 74%</td>
<td></td>
<td>✓</td>
<td>✗</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Wild-type TTR amyloidosis 10%</td>
<td></td>
<td>✓</td>
<td>❌</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
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<tr>
<td>80% men, isolated heart</td>
<td></td>
<td>✓</td>
<td>❌</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Hereditary ATTR amyloidosis 7%</td>
<td></td>
<td></td>
<td>❌</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
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~25% of patients with wild-type TTR cardiac amyloidosis have a monoclonal protein


- Proteomics-MS\(^1,2\)
- Immuno-EM\(^3\) – Immunohistochemistry\(^4\)
- \(^{99}\)TC-DPD/HMDP/PYP scintigraphy\(^5\)
- DNA analysis

1. Vrana et al, Blood 2009
3. Arbustini et al, Amyloid 2002
5. Gillmore et al, Circulation 2005
Therapy

Suppressing the synthesis of the amyloid protein provides the highest degree of therapeutic efficacy

• **AIM**: 1. **Rapid** and **profound decrease** of the amyloid precursor
  2. Removal of fibrils

• **GOAL**: Organ (cardiac) function improvement → survival extension

• **CHALLENGE**: Frail patients in need of rapid and deep responses → risk stratification
  o Patient characteristics (severity of cardiac damage)
  o Clone biology (burden of FLC, PC%, iFISH)
  **supportive therapy** to sustain the function of the organs involved

NT-proBNP (>332 ng/L) and troponin I (>0.1 ng/mL)
Stage IIIb patients have NT-proBNP > 8500 ng/L\(^1\)

1. Wechalekar et al, Blood 2013
**Hematologic response**

- **CR:** negative s&u IFE + normal FLCR
- **VGPR:** dFLC <40 mg/L
- **PR:** dFLC decrease >50%
- **Low-dFLC response:** dFLC <10 mg/L

**Cardiac response**

- NT-proBNP decrease >30% & >300 ng/L

**Renal response**

- Proteinuria decrease >30%

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**Validated criteria for early (3 & 6 months) assessment of response**

<table>
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<tr>
<th>Response</th>
<th>Definition</th>
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</table>
| Hematologic | CR: negative s&u IFE + normal FLCR  
VGPR: dFLC <40 mg/L  
PR: dFLC decrease >50%  
Low-dFLC response: dFLC <10 mg/L |
| dFLC 20-50 mg/L |          |
| Cardiac | NT-proBNP decrease >30% & >300 ng/L |
| Renal | Proteinuria decrease >30% |

**Hematologic CR → 54% Cardiac response**

**Renal response**

**Hematologic CR → 68% Renal response**

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BMDex vs. MDex in AL amyloidosis

A phase III trial of BMDex vs. MDex

**Response**

<table>
<thead>
<tr>
<th>Response</th>
<th>MDex (56 pts)</th>
<th>BMDex (53 pts)</th>
<th>P</th>
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<tbody>
<tr>
<td>Overall HR</td>
<td>32 (57%)</td>
<td>43 (81%)</td>
<td>0.005</td>
</tr>
<tr>
<td>CR</td>
<td>11 (20%)</td>
<td>12 (23%)</td>
<td>0.440</td>
</tr>
<tr>
<td>VGPR</td>
<td>11 (20%)</td>
<td>21 (39%)</td>
<td>0.018</td>
</tr>
<tr>
<td>PR</td>
<td>10 (17%)</td>
<td>10 (19%)</td>
<td>0.543</td>
</tr>
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**Treatment of intermediate-risk patients (~45%)**
(ineligible for ASCT, stages I-IIIa)

- **BMDex**
- **(Cy)BorD**, stem cell sparing, preferred in renal failure and in patients with gain 1q21
- **MDex**, preferred in case of neuropathy and in patients with t(11;14)

*X* Kastritis, *et al.* ASH 2016, Abstr. #646

*Palladini & Merlini. Blood 2016*
Front-line therapy in AL amyloidosis

• **Risk-adapted treatment** possibly in the framework of clinical trials
• **Frequent assessment of response** based on FLC and biomarkers of organ function

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<th>Fit (15-25%)</th>
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| age < 65 years (> for fit elderly)  
NT-proBNP < 5000 ng/L,  
cTnT < 0.06 ng/mL,  
PS 0–2,  
eGFR > 50 mL/min per 1.73 m²  
NYHA class < III, EF > 45%,  
sBP > 90 mm Hg (standing),  
DLCO > 50% |
| **ASCT MEL 200¹**: CR/VGPR 50-60% |
| • CyBorD induct.² if BMPC>10%³  
• BDex if < CR⁴ |

1. Tandon et al, *Bone Marrow Transplant*. 2017  
2. Minnema et al, *EHA22 - S411*  
4. Landau et al, *Leukemia 2017*
Relapsing patients

When to start treatment?
Second line treatment should start promptly at progression of FLC, before cardiac progression has occurred.

Which regimen?
- Bortezomib-exposed: *lenalidomide, pomalidomide*
- Bortezomib-naïve: bortezomib, ixazomib
- Alkylator-naïve: ASCT, MDex
- Daratumumab

Palladini et al, *Blood* 2017
Treatment of relapsing/refractory patients

Pomalidomide produces rapid and profound responses

28 patients previously exposed to bortezomib, alkylators, and other IMiDs
3 patients received pomalidomide 2 mg/d, 25 patients 4 mg/d – Dex 20-40 mg/wk
15 patients had grade 3 to 4 AE mainly fluid retention and infection

Median time to response: 1 mo

HR 68%, ≥VGPR 29%

• Immune therapies
  anti-clone
  anti-amyloid
Infections:
- 5 patients with pneumonia admitted to ICU all (cardiac AL)
- 7 patients reported upper respiratory tract infections without need for hospital admission (one patient with RSV + influenza)
NEOD001 Phase 1/2 Trial in AL amyloidosis

- 69 patients
- NEOD001 24 mg/kg every 28 days
- Grade ≥3 in 2 patients (fatigue and anemia)

Peripheral Neuropathy Expansion Cohort (N = 11)
9 responders (82%)  2 progressors (18%)

Phase 3: The VITAL Study (NCT02312206)
Phase 2b: The PRONTO Study (NCT02632786)

Gertz et al, J Clin Oncol 2016
Gertz et al, ASH 2016 Abstr. #644
Liedtke et al, ASH 2016 Abstr #647
Prothena Discontinues Development of NEOD001 for AL Amyloidosis

- Phase 2b PRONTO study did not meet its primary or secondary endpoints
- Phase 3 VITAL Amyloidosis Study being discontinued based on futility analysis
Immunotherapy: Anti-SAP antibodies

Deplete plasma of SAP using CPHPC

Some SAP still remains on amyloid deposits

Give anti-SAP antibody to target amyloid deposits

Phase 1 trial involving 15 patients, 8 AL
Single dose anti-SAP Ab (up to 650 mg)
Improved SAP scan and liver function

Progressive amyloid load reduction with repeat dosing

Anterior SAP scintigraphy scans of systemic AL amyloidosis patient who received two treatments with CPHPC + anti-SAP antibody


Richards et al, *NEJM* 2015;373:1106-14
Phase Ia/b Study of Chimeric Fibril-Reactive Monoclonal Antibody 11-1F4 (CAEL-101) in Patients with AL Amyloidosis

8 patients in phase 1a and 19 patients in phase 1b
Patients with relapsed/refractory organ disease
who received prior anti-clone therapy

Phase 1°
Single IV infusion at Week 1
Dose: 0.5 mg/m² to 500 mg/m²

Phase 1b
Weekly IV infusion for 4 weeks at Weeks 1-4
Dose: 0.5, 5, 10, 50, 100, 250, and 500 mg/m²

Wall et al, Blood 2010

Lentzsch et al, ASH 2017 Abstr. 509
Targeted therapies in AL amyloidosis: Current and future directions

**Anti-plasma cell therapies**
- ASCT
- Bortezomib-based
- MDex
- IMiDs
- Daratumumab
- Ixazomib
- Carfilzomib
- Bendamustine
- Venetoclax
- T-cell based therapy

**LC stabilizers**
- Doxycycline
- Metal binding comp.
- p38MAPK inhibitors

** EGCG**

**Organ dysfunction Reduced survival**
- LV1-44
- KV1-33
- LV6-57

**Matrix components, metals, shear forces, endoproteases, cell interactions**

**Chaperones**

**Toxicity**

**Mass action**

**Combination therapy** → accelerate recovery of cardiac function → ↑ OS

Conclusions

- New horizons in systemic amyloidosis
- Biomarkers and imaging → earlier diagnosis
- New drugs targeting key pathogenic events can preserve cardiac function
- In the near future the treatment of systemic amyloidosis will include the combination of agents targeting critical steps of the amyloid cascade
- National and international collaboration both in basic and clinical research will foster understanding and improve the care
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