Light-chain amyloidosis Overview

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Overview

• Focus on:
  – Early diagnosis
  – Risk assessment
  – Therapeutic strategy

• Clinical cases
Spectrum of the possible progression of MGUS

M-protein–related diseases

AL amyloidosis
MGRS (MIDD, ITG, FS, etc.)
Other M-protein-related diseases

MGUS

Low-risk MGUS
Intermediate- high-risk MGUS
Low-risk SMM
High-risk SMM
Active MM

End-organ damage (CRAB)

EMM, PCL

Tumor progression

Irreversible end-organ damage

Accumulation of genetic, epigenetic and microenvironmental abnormalities

Survival

Immunoglobulin light chain amyloidosis (AL)
Incidence 10 patients/million/year – 10% of MM patients

Misfolded FLC

Interactions with target organs

SAP

Amyloid fibrils

Small dangerous clone\(^1\)
(BMPC 7%)
53% LC only 75% \(\lambda\)

proteotoxicity structural damage

\(\lambda^1\)\(^*\)

\(\lambda^6\)\(^**\)

Heart 74% CHF 47%
Kidney 65% Nephrotic s. 42% Renal failure 45%
Liver 17%
GI 8%
Soft tissues 17%
ANS 14%
PNS 15%

\(^{1}\)Merlini & Stone, Blood 2006

Survival of 628 patients with AL amyloidosis diagnosed between 2004 and 2011 at the Pavia Amyloid Research and Treatment Center.

- Renal involvement without cardiac involvement (123 patients)
- Overall population (628 patients)
- Cardiac involvement (473 patients)

- Median survival of the overall population: 42 months
- Median survival of patients with cardiac involvement: 20 months
- ~20% died by 3 months

Early diagnosis is vital.
Monitoring amyloid load SAP scan

TcDPD and Tc-PYP scintigraphy

AL TcDPD ATTR

Rapezzi et al, JACC Img 2011

Bokhari et al, Circ Cardiov Img 2013

Cardiac MR-T1 mapping

Maceira et al, Circulation 2005
Banypersad et al. Circ Cardiovasc Img 2013
Fontana et al. JACC Cardiovasc Img 2014

Echocardiography is the cornerstone for the diagnosis and management of cardiac amyloidosis

Buss et al, JACC 2012
When to suspect amyloidosis

- Concentric “hypertrophy“, “granular sparkling”, low voltages at ECG

→ advanced stage of the disease!
→ need for more sensitive markers of organ involvement
Serum N-terminal Pro-Natriuretic Peptide type B (NT-proBNP) is a sensitive marker of myocardial dysfunction in AL amyloidosis.

Diagnostic sensitivity: 100%  
It can detect heart involvement several months before symptoms

<table>
<thead>
<tr>
<th>Organ or syndrome</th>
<th>Present in</th>
<th>Early “red flags”</th>
</tr>
</thead>
</table>
| Heart             | 74%        | NT-proBNP >332 ng/L (100% sensitivity)  
BNP >73 ng/L (89% sensitivity) |
| Kidney            | 65%        | Urinary albumin > 0.5 g/day |
June 2011 Male, 59 y
IgG_κ (10 g/L), normal CBC, calcium, creatinine, proteinuria 0.12 g/24h,
**FLC_κ 123 mg/L, dFLC 99 mg/L, κ/λ ratio 5.1**
urine IFE positive for κ LC
BMPC 7%, no cytogenetic abnormalities
Normal MRI and low-dose CT
MGUS of low-intermediate risk → annual follow up
**NT-proBNP included in the follow-up (25 ng/L)**
Early diagnosis is possible in patients with MGUS

June 2012

IgG\textsubscript{\kappa} (14 g/L), normal CBC, calcium, creatinine
FLC\textsubscript{\kappa} 157 mg/L, dFLC 124 mg/L, \kappa/\lambda ratio 4.7
NT-proBNP 475 ng/L – asymptomatic
echo: IVS 11 mm, PW 11 mm, EF 65%
proteinuria 0.42 g/24h, creatinine 0.75 mg/dL
abdominal fat: positive
typing of amyloid deposits: \kappa by IEM and MS

anti-\kappa

Treatment ?
Early diagnosis is possible in patients with MGUS

- ASCT
- CyBorD + ASCT
- BDex
- MDex
- LenDex

The patient was treated with CyBorD

December 2012  After 4 cycles of CyBorD
- negative serum and urine IFE
- FLC\(_\kappa\) 18 mg/L, dFLC 4 mg/L, \(\kappa/\lambda\) ratio 1.3
- NT-proBNP 174 ng/L, cTnI 0.01 ng/mL
- echo: IVS 11 mm, PW 11 mm, EF 65%

**Complete response → SC harvesting → follow-up**

October 2013  Positive serum and urine IFE,
- FLC\(_\kappa\) 85 mg/L, dFLC 57 mg/L, \(\kappa/\lambda\) ratio 3.0
- NT-proBNP 395 ng/L, cTnI 0.01 ng/mL
- echo: IVS 11.5 mm, PW 11 mm, EF 61%

December 2013  ASCT (M 200) uneventful
March 2014  Complete response, all markers normal, back to full work
Early detection of end-organ damage in AL amyloidosis

50% with complete Ig→70% preceded by MGUS with abnormal FLC ratio lasting a median of 4 years

Subjects with intermediate- and high-risk MGUS with abnormal FLC ratio should be followed annually for life, measuring¹:

- NT-pro-BNP or BNP
- urine albumin

at MGUS presentation and at each follow-up visit may help in detecting AL amyloidosis earlier

If these tests are positive a procedure to diagnose AL amyloidosis² should be promptly pursued

²Merlini G, Seldin DC, Gertz MA. J Clin Oncol 2011;29:1924-33
Diagnosis of amyloidosis relies on Congo red staining of tissue biopsy

Tissue of choice: abdominal fat
sensitivity 88% + BM biopsy 95% specificity 97% in AL amyloidosis

If negative
Biopsy of the labial minor salivary glands\(^2\) (89% sensitivity in ATTR)\(^3\)
Duodenal biopsy in AA\(^4\)

If negative
Biopsy of the involved organ (kidney, liver, heart, nerve): beware of the hemorrhagic risk

\(^2\)Caporali et al, Arthritis Rheum. 2008;59: 714-20
\(^3\)Coelho et al, EFNS 2011
\(^4\)Miyaoka et al. Dig Endosc 2011;23:157-65
### Typing of amyloidosis is essential for the choice of therapy

<table>
<thead>
<tr>
<th>Amyloid type</th>
<th>Heart</th>
<th>Kidney</th>
<th>Liver</th>
<th>PNS</th>
<th>ANS</th>
<th>Soft tiss.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL amyloidosis</td>
<td>++</td>
<td>++</td>
<td>+</td>
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<tr>
<td>Hereditary ATTR amyloidosis</td>
<td>++</td>
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<tr>
<td>Hereditary AApoAI amyloidosis</td>
<td>++</td>
<td>+</td>
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<td>-</td>
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<tr>
<td>AA (reactive) amyloidosis</td>
<td>±</td>
<td>++</td>
<td>+</td>
<td>-</td>
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<tr>
<td>Senile systemic amyl. (wtTTR)</td>
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- **Up to 10% of patients with hereditary amyloidosis have a monoclonal gammopathy**
- **21% of patients with SSA have a monoclonal gammopathy:** TcDPD and Tc-PYP scintigraphy are usually positive in senile amyloidosis

Seldin D C, Sanchorawala V Blood 2012;119:1795-1796

**Coupling proteomics with histology: analysis of laser-dissected amyloid**


**Analysis of intact (abdominal fat) tissue: Shotgun-proteomics approach**


### Identification of amyloid based on (semi)quantitative evaluation

<table>
<thead>
<tr>
<th>Case</th>
<th>IEM-confirmed diagnosis</th>
<th>IgG, IgA</th>
<th>TTR</th>
<th>SAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>74</td>
<td>ALA</td>
<td>15</td>
<td>6</td>
<td>6</td>
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<tr>
<td>72</td>
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<td>76</td>
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<td>88</td>
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<td>72</td>
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<td>4</td>
<td>1156</td>
<td>6</td>
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<td>0</td>
<td>2</td>
<td>6</td>
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Proteins contained in the amyloid deposits are specifically analyzed.
When To Use Proteomics: ~20% of cases

- Two possible amyloid proteins in 1 patient, presence of a monoclonal protein in:
  - Elderly male patients with isolated cardiac involvement (SSA, ATTR)
  - Patients with only peripheral neuropathy (ATTR)
  - Patients with only kidney and inflammatory syndromes (AA)
Assessing the monoclonal disease

• Serum and urine immunofixation + serum FLC*

• Bone marrow plasma cell evaluation (Immunofluor.)
  PC% > 10% is associated with a poor prognosis§

• Cytogenetics and fluorescence in situ hybridization

• Bone imaging (low-dose CT, MRI)

Patients with AL amyloidosis are fragile: Risk stratification
Serum Cardiac Troponins and N-Terminal Pro-Brain Natriuretic Peptide: A Staging System for Primary Systemic Amyloidosis

Angela Dispensieri, Morie A. Gertz, Robert A. Kyle, Martha Q. Lacy, Mary F. Burritt, Terry M. Therneau, Philip R. Greipp, Thomas E. Witzig, John A. Lust, S. Vincent Rajkumar, Rafael Fonseca, Steven R. Zeldenrust, Christopher G.A. McGregor, and Allan S. Jaffe

Revised Prognostic Staging System for Light Chain Amyloidosis Incorporating Cardiac Biomarkers and Serum Free Light Chain Measurements


**Standard staging system**

NT-proBNP >332 ng/L, cTnl >0.1 ng/mL

**Revised staging system**

NT-proBNP >1800 ng/L, cTnl >0.07 ng/L, dFLC >180 mg/L

Two main prognostic determinants:
- FLC burden
- Severity of heart involvement
A European collaborative study of treatment outcomes in 346 Patients with Stage III AL amyloidosis

Wechalekar, Schönland ....., Merlini, and Palladini

Blood. 2013;121:3420-7

NT-proBNP < 8500 ng/L
Median 17 months
HR:42%, CR 18%

NT-proBNP > 8500 ng/L
Median 4.6 months
HR:18%, CR 2%

«Very high risk»
○ NT-proBNP >8500 ng/L
○ SBP <100 mmHg
Patients with serum troponin T >0.06 ng/mL or NT-proBNP >5000 pg/mL (not on dialysis) **should not** be considered candidates for SCT because of early mortality.

Refinement in patient selection to reduce treatment-related mortality from SCT in amyloidosis

New criteria for response to treatment in immunoglobulin light chain amyloidosis based on free light chain measurement and cardiac biomarkers: impact on survival outcomes.


<table>
<thead>
<tr>
<th></th>
<th>aCR</th>
<th>Negative s. &amp; u.IFE, normal FLR</th>
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<tbody>
<tr>
<td></td>
<td>VGPR</td>
<td>dFLC &lt;40 mg/L</td>
</tr>
<tr>
<td></td>
<td>PR</td>
<td>dFLC decrease ≥50%</td>
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<tr>
<td></td>
<td>NR</td>
<td>other</td>
</tr>
</tbody>
</table>

dFLC: Involved FLC – uninvolved FLC

New cardiac response criteria
reduction of NT-proBNP >30% and >300 ng/L

Renal insufficiency and IMiDs may alter NT-proBNP metabolism

Renal response is usually delayed (median 11 months); new criteria under validation
It is possible to recover the organ function and extend survival through prompt reduction of the amyloidogenic protein combined with novel approaches derived from disease mechanisms.
Therapy development in AL amyloidosis

5. Parmar et al, BMT 2014
Patients with AL amyloidosis undergoing ASCT have superior outcomes as compared to patients with MM.

Seenithamby et al, *Bone Marrow Transplant*. 2013;48:1302-7

"This difference suggests very different plasma cell biology between the two diseases."
**Regimen** | HR (CR) | OR | Common SAEs | 100-day mortality | PFS / OS (y)
---|---|---|---|---|---
MDex | 67% (33%) | 48% | Overall 11% | 4% | 3.8 / 5.1

**MDex in the treatment of intermediate-risk patients: an update**

- 119 patients, median age 64y
- Deaths at 3 months 0%, SAE 16%

**Hematologic Response:**
- CR: 31%
- VGPR: 29%
- PR: 16%
- NR: 24%

**Organ response**
- Heart: 37%
- Kidney: 24%

*median survival 7.3 years*
### Current treatment options for AL amyloidosis
**IMiDs-based therapy and novel agents**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No (front-I)</th>
<th>HR (CR)</th>
<th>Org. Rsp</th>
<th>Common SAEs</th>
<th>100-d mortal.</th>
<th>PFS / OS (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTD</td>
<td>75 (41%)</td>
<td>74% (21%)</td>
<td>27%</td>
<td>Sedation 40% Fluid retent. 21%</td>
<td>4%</td>
<td>1.7 / 3.4</td>
</tr>
<tr>
<td><strong>Wechalekar 2007</strong></td>
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<tr>
<td>LDex⁺</td>
<td>22 (41%)</td>
<td>41%</td>
<td>23%</td>
<td>Overall 86% Neutropenia 45%</td>
<td>18%</td>
<td>1.6 / -</td>
</tr>
<tr>
<td><strong>Dispenzieri 2007</strong></td>
<td></td>
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<tr>
<td>CLD#</td>
<td>35 (11%)</td>
<td>60% (11%)</td>
<td>31%</td>
<td>Overall 74% Neutropenia 40%</td>
<td>9%</td>
<td>2.4 / 3.1</td>
</tr>
<tr>
<td><strong>Kumar 2012</strong></td>
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<tr>
<td>MLD</td>
<td>26 (100%)</td>
<td>58% (23%)*</td>
<td>50%</td>
<td>Overall 81% Neutropenia 11%</td>
<td>-</td>
<td>@2y 54% / 81%</td>
</tr>
<tr>
<td><strong>Moreau 2010</strong></td>
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<tr>
<td>PomDex§</td>
<td>33 (0)</td>
<td>48% (3%)</td>
<td>15%</td>
<td>Neutropenia 30%</td>
<td>3%</td>
<td>1.2 / 2.3</td>
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<tr>
<td><strong>Dispenzieri 2012</strong></td>
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<tr>
<td>BendaDex</td>
<td>36 (14%)</td>
<td>47% (3%)</td>
<td>17%</td>
<td>Overall 33% Neutropenia 17%</td>
<td>5%</td>
<td>@3y -/65%</td>
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<tr>
<td><strong>Palladini 2012 ASH</strong></td>
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</table>

*(42% with full-dose L) §also Palladini et al, ASH 2013
Current treatment options for AL amyloidosis
Proteasome inhibitor-based therapy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No (front-I)</th>
<th>HR (CR)</th>
<th>Org. Rsp</th>
<th>Common SAEs</th>
<th>100-d mortal</th>
<th>PFS / OS (y)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortez</td>
<td>70 (0)</td>
<td>68% (29%)</td>
<td>29% K</td>
<td>Fatigue, Thrombocytn, Vomiting</td>
<td>3%</td>
<td>@1y 74%/93%</td>
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<tr>
<td><em>Reece 2011</em></td>
<td></td>
<td></td>
<td>13% H</td>
<td>Diarrhea</td>
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</tr>
<tr>
<td>BDex</td>
<td>94 (19%)</td>
<td>71% (25%)</td>
<td>30%</td>
<td>PN Edema Orthost. hyp.</td>
<td>3%</td>
<td>2/@1y 76%</td>
</tr>
<tr>
<td><em>Kastritis 2010</em></td>
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</tr>
<tr>
<td>CyBorD*§¥</td>
<td>43 (47%)</td>
<td>81% (65% fl)</td>
<td>46%</td>
<td>19% discontinued (PN in 14%)</td>
<td>0</td>
<td>@2y 53% / 98%</td>
</tr>
<tr>
<td><em>Venner 2012</em></td>
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<tr>
<td>Ixazomib</td>
<td>20 (0)</td>
<td>55% (10%)</td>
<td>30% H</td>
<td>Fatigue Thrombocytn</td>
<td>5%</td>
<td>-/-</td>
</tr>
<tr>
<td><em>Merlini ASH 2012</em>**</td>
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</table>


Median times to first and best HR: 2.1 and 3.2 months in the 1.6 mg/m² QW group, and 0.7 and 1.2 months in the 1.3 mg/m² BW group
Therapy is highly individualized and must be risk-adapted based on cardiac biomarkers and response-tailored

- Treatment endpoint: at least VGPR

- Hematologic and cardiac response should be assessed frequently, every 1-2 cycles (or three months after ASCT)

- Rapid switch if no response

- Therapy can be continued for 1-2 cycles beyond best response for consolidation

<VGPR → Bortez if unexposed and no severe neuropathy
Len, Pom\textsuperscript{1,2}, Benda\textsuperscript{3} in resist. to alkyl/ bortez/ thal
Len requires monitoring renal function
New drugs, such as Ixazomib\textsuperscript{4}

\textsuperscript{1}Dispenzieri et al, Blood 2012;119 :5397-404 .\textsuperscript{2}Palladini et al ASH 2013 .\textsuperscript{3}Merlini et al, Blood. 2012;120(21) Abstr 4057 - \textsuperscript{4}Merlini et al, Blood 2012;120(21) Abstr 731
Proposed algorithm for treating AL amyloidosis

Assess eligibility for SCT

eligible

Age<70 Creatinine <1.8 mg/dl
Troponin T <0.06 microg/l
NT-proBNP <5000 ng/l
Systolic BP >100 mmHg

20%

CyBorD, BDex?

Stem cell transplantation

NT-proBNP <8500 ng/l
PS 1-2

60%

Mel-Dex
(CyBorD – Bor-Mel-Dex)

NT-proBNP >8500 ng/l
SBP <100 mmHg

20%

Cautious chemotx
dose-attenuated
close monitoring

Novel approaches

Agents not previously used:
Len, Pom, Ixazom, Benda

Clinical Trials

≥VGPR

Observe

Consolidation: bortezomib based

<VGPR

progr.

Adapted from Merlini et al, Expert Rev. Hematol 2014;7:143-56
*Huang et al, BMC Med 2014;12:2
**Frontline treatment of AL amyloidosis patients and 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 0.11-0.22 mg/Kg on Days 1-4&lt;br&gt;Dex 20 mg/m² on Days 1-4</td>
<td>40</td>
<td>Median cTnl 0.12 ng/mL&lt;br&gt;Median BNP 1000 ng/L&lt;br&gt;85% class II or higher</td>
<td>58% / 13%</td>
<td>-</td>
<td>23%</td>
<td>-</td>
<td>10.5 months</td>
</tr>
<tr>
<td>Palladini, et al.</td>
<td>MTDex&lt;br&gt;M 0.22 mg/Kg&lt;br&gt;T 100 mg/Day&lt;br&gt;Dex 20 mg on Days 1-4</td>
<td>22</td>
<td>Stage III: 73%&lt;br&gt;Median NT-proBNP 11282 ng/L</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 MDex&lt;br&gt;M 16 mg/m² on Day 1&lt;br&gt;Dex 40 mg on Days 1-4</td>
<td>61</td>
<td>Stage III: 53%&lt;br&gt;Median NT-proBNP 4420 ng/L</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>MDex&lt;br&gt;T combinations&lt;br&gt;B combinations&lt;br&gt;L combinations</td>
<td>154</td>
<td>Stage III: 100%&lt;br&gt;Median NT-proBNP 9106 ng/L&lt;br&gt;NT-proBNP &gt;8500 ng/L in 52%</td>
<td>52%</td>
<td>40% / 15%</td>
<td>12%</td>
<td>30%</td>
<td>7.1 months&lt;br&gt;(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&lt;br&gt;M 0.18 mg/Kg on Days 1-4&lt;br&gt;L 10 mg on Days 1-21&lt;br&gt;Dex 40 mg/week</td>
<td>25</td>
<td>Stage III: 36%&lt;br&gt;Median NT-proBNP 2443 ng/L</td>
<td>20%</td>
<td>58% / 8%</td>
<td>9%</td>
<td>40%</td>
<td>58% at 12 months&lt;br&gt;(1.8 months in stage III)</td>
</tr>
</tbody>
</table>

- Understand the mechanisms of cardiac damage
- Develop new therapies
p38MAPK mediates AL-LC induced ROS, cellular dysfunction, and cardiomyocytes death

Cardiotoxic light chains

p38α MAPK

ROS (Oxidative Stress)

Cellular Dysfunction  Cell Death

SB203580, p38 MAPK inhibitor

Shi et al, Proc Natl Acad Sci U S A. 2010;107:4188-93
Guan et al., Basic Res Cardiol. 2013;108(5):378
Cardiotoxic light chains specifically inhibit the muscular pumping motions of the *C. elegans* pharynx (ortholog of vertebrate heart).

**Significant increase of the MitoSOX fluorescence, indicative of an oxidant burden enhancement**

- Vehicle
- Myeloma LC
- AL-heart LC

6 non cardiotoxic amyloid LC
8 cardiotoxic amyloid LC (3 rec)
5 control MM LC

Drugs with antioxidant activity revert the pharyngeal pumping inhibition caused by cardiotoxic LC

Novel approaches to treatment of AL amyloidosis

Novel agents (MoAb Elotuzumab, Daratumumab)\(^1\), \(^2\) and combinations with synergistic mechanisms of action

Conclusions

• **Earlier diagnosis** remains the keystone for improving the care of AL amyloidosis:
  - Routine adoption of checking NT-proBNP levels and urine albumin during monitoring of patients with MGUS may help early diagnosis

• Therapy is highly individualized and must be **risk-adapted** and **response-tailored**

• Novel therapeutic approaches are needed for patients with advanced amyloid cardiomyopathy

**Phase III trials necessary through international collaboration:**
  - EMN-03 European Network and Centers in Australia for Phase III trial comparing MDex vs BortezMDex
Acknowledgements

European Network - EMN-03 Phase III trial comparing MDex vs BortezMDex

Thank you!

Amyloidosis Research and Treatment Center
Dept. Molecular Med.
Giovanni Palladini
Laura Obici
Andrea Foli
Mario Nuvolone
Paola Rognoni
Francesca Lavatelli
Paolo Milani
Loredana Marchese
Stefano Perlini
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