Light Chain (AL) Amyloidosis Diagnosis & Management

Michael Rosenzweig, MD
How The Experts Treat Hematologic Malignancies
Disclosures

• Speakers Bureau:
  – Celgene
Amyloidosis: Lecture Outline

- Definition & Diagnosis
  - when to suspect and how to confirm
- Classification: subtype impacts treatment
- Staging
- Amyloid related organ disease
  - Involvement & Response Criteria
- Treatment & Management
  - Anti-plasma cell
  - Anti-amyloid
Amyloidosis: Protein Conformation/folding Disorder

- Precursor proteins misfold and aggregate to form β-Strands
- Predominant anti-parallel arrangement of β-Strands \( \rightarrow \) β-sheets \( \rightarrow \) Fibrils
- Fibril structure allows for Congo red staining and apple green birefringence
  - Amyloid fibrils with non-fibrillar constituents (GAGs and SAP) deposit in organs and tissues (extracellular deposition)
  - Progressively interfere with organ structure/ function
- Dozens proteins known to form amyloid

## Classification of Amyloidosis

<table>
<thead>
<tr>
<th>Type of amyloidosis</th>
<th>Precursor protein</th>
<th>Clinical Presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (primary)</td>
<td>κ or λ light chain</td>
<td>Systemic or localized</td>
</tr>
<tr>
<td>AH</td>
<td>Ig heavy chain</td>
<td>Systemic or localized</td>
</tr>
<tr>
<td>AA (secondary)</td>
<td>Serum amyloid A protein</td>
<td>Renal (most common) Chronic inflammatory conditions, hereditary in familial periodic fever</td>
</tr>
<tr>
<td>ATTR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutated TTR (familial)</td>
<td>Mutant TTR</td>
<td>Peripheral/autonomic neuropathy, CMY, vitreous opacities</td>
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<tr>
<td>Wild-type (senile)</td>
<td>Normal TTR</td>
<td>Restrictive CMY; carpel tunnel syndrome</td>
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<tr>
<td>LECT2</td>
<td>Leukocyte chemotactic factor 2</td>
<td>Renal (acquired)</td>
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<tr>
<td>Aβ2M</td>
<td>B2-microglobulin</td>
<td>Carpel Tunnel, arthropathy</td>
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<td>Other Hereditary</td>
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<td>Afib</td>
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<tr>
<td>Alys</td>
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<tr>
<td>ApoA1</td>
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<tr>
<td>Agel</td>
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<tr>
<td>Fibrinogen alpha</td>
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<tr>
<td>Lysozyme</td>
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<tr>
<td>A-1 Apolipoprotein</td>
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<td></td>
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<tr>
<td>Gelsolin</td>
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<td></td>
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<tr>
<td>Renal (most common)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (most common)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cranial neuropathy</td>
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</tr>
</tbody>
</table>
When to Suspect Amyloidosis

• Any patient and unexplained...
  – Shortness of breath
  – Nephrotic syndrome
  – Restrictive cardiomyopathy
  – **Fatigue** (Most Common Presenting Symptom)
    • Merlini et al. Amyloidosis Center
  – Autonomic or sensory/motor neuropathy
  – GI dysmotility
  – Hepatomegaly or increased alkaline phosphatase
  – Unintentional Weight loss

• Especially in the setting monoclonal gammopathy
Diagnosis: Tissue is the Issue

• If you don’t think it, you can’t diagnose it!
• Early diagnosis is critical

• Fat pad Aspiration (positive in 70%)

• Biopsy involved organ
  - Renal
  - Endomyocardium
  - Liver
  - Endoscopic GI

• BM + Fat Pad will diagnosis 85% of AL cases
  - Gertz et al. Leuk Lymphoma 2010

Kidney biopsy
Endomyocardial biopsy

Amyloid 2007;14:179
NEJM 2002;346:1786
Fat Pad Aspiration

1. Two areas 7-10cm lateral of the umbilicus are cleaned in a sterile fashion
2. Anesthetize both areas using a 5 ml syringe, a 22 gauge needle and 1% lidocaine
3. Use a 16 Gauge needle and 10cc syringe
4. Insert needle medially toward the umbilicus parallel to the table surface
5. Move needle in a semi circular fashion while applying continuous negative pressure
6. Withdraw needle from skin with continued negative pressure
Fat Pad Aspirate

BU Video: https://www.youtube.com/watch?v=tctYTmxd9gQ

gross tissue
Congo red stain
apple green birefringence
Subtyping Amyloid: Type Effects Treatment!

- Determine the precursor protein
- Tissue-based Subtyping
  - Immunohistochemistry (unreliable in AL)
  - Immunoelectron microscopy (Immunogold)
  - Immunofluorescence
  - Liquid chromatography- tandem mass spectrometry
    - Gold Standard
- MGUS: common pre-malignant condition
  - 3.2% of the population over 50

Amyloid Subtype: Must be known!
# Laser Microdissection Mass Spectrometry

![Image](image_url)

<table>
<thead>
<tr>
<th># Accession</th>
<th>MW</th>
<th>Control</th>
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<th>2</th>
<th>3</th>
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<td>1 ALBU_HUMAN</td>
<td>69 kDa</td>
<td>100% (36)</td>
<td>100% (35)</td>
<td>100% (36)</td>
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<td>2 APOE_HUMAN</td>
<td>36 kDa</td>
<td>100% (19)</td>
<td>100% (17)</td>
<td>100% (18)</td>
<td>100% (17)</td>
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<td>100% (17)</td>
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<td>4 KAC_HUMAN</td>
<td>12 kDa</td>
<td>100% (7)</td>
<td>100% (8)</td>
<td>100% (7)</td>
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<tr>
<td>5 APOA4_HUMAN</td>
<td>45 kDa</td>
<td>100% (15)</td>
<td>100% (19)</td>
<td>100% (17)</td>
<td>100% (13)</td>
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<tr>
<td>6 SAMP_HUMAN</td>
<td>25 kDa</td>
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<td>7 C4BP_HUMAN</td>
<td>67 kDa</td>
<td>100% (11)</td>
<td>100% (10)</td>
<td>100% (12)</td>
<td>100% (10)</td>
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<td>8 HBB_HUMAN</td>
<td>16 kDa</td>
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<td>100% (9)</td>
<td>100% (7)</td>
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<td>9 CLUS_HUMAN</td>
<td>52 kDa</td>
<td>100% (10)</td>
<td>100% (7)</td>
<td>100% (8)</td>
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<td>10 CO6A3_HUMAN</td>
<td>344 kDa</td>
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<td>31 kDa</td>
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<td>100% (5)</td>
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<td>13 TRFE_HUMAN</td>
<td>77 kDa</td>
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<td>100% (6)</td>
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<td>14 HBA_HUMAN</td>
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<td>15 CO3_HUMAN</td>
<td>187 kDa</td>
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<td>100% (5)</td>
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<table>
<thead>
<tr>
<th>Protein</th>
<th>Sample</th>
<th>Probability</th>
<th>Unique Peptides</th>
<th>Unique Spectra</th>
<th>Total spectra</th>
<th>% Coverage</th>
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</thead>
<tbody>
<tr>
<td>Ig kappa chain C region</td>
<td>Sample 1</td>
<td>100%</td>
<td>7</td>
<td>10</td>
<td>53</td>
<td>80%</td>
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<tr>
<td>Ig kappa chain C region</td>
<td>Sample 2</td>
<td>100%</td>
<td>8</td>
<td>11</td>
<td>53</td>
<td>67%</td>
</tr>
<tr>
<td>Ig kappa chain C region</td>
<td>Sample 3</td>
<td>100%</td>
<td>7</td>
<td>11</td>
<td>58</td>
<td>67%</td>
</tr>
<tr>
<td>Ig kappa chain C region</td>
<td>Sample 4</td>
<td>100%</td>
<td>8</td>
<td>12</td>
<td>61</td>
<td>80%</td>
</tr>
</tbody>
</table>

Vrana et al. Blood 2009
AL Amyloidosis: Light Chain Amyloidosis

- Most common form of systemic amyloidosis
  - Localized amyloidosis: light chain
- Two part disease:
  - Clonal B cell disorder
    - 98% plasma cell dyscrasias
    - 2% lymphomas, most common IgM
  - Amyloid related organ disease
- Rare disease: Incidence of 5-12 persons/million/year

Br J Haematol 2004;124:309
JNCCN 2007;5:179
The Amyloidogenic B-cell Clone

- Small but dangerous
- Similar phenotype to MM but not exactly?
  - BCMA and CS1 expression
    » Rosenzweig et al. Cytotherapy 2017
- FISH
  - T(11;14): most common observed abnormality
    • 40-60% of patients
  - Gain of 1q21: 25% of patients
AL: Plasma Cell Evaluation

- Bone marrow aspirate and biopsy
  - CD 138+ plasma cells
  - Kappa/lambda IHC staining
  - Congo red stain (+ 60% of BMs)
    - Mostly λ restriction: κ to λ ratio ~1:4
- Serum Protein Electrophoresis (SPEP)
  - M-spike uncommon
  - 75% by S-IF,
- 24 hour urine and UPEP
  - 85% by U-IF
- Serum Free Light Chains
  - > 95% by serum free light chains
Plasma Cell Dyscrasias

Light Chain Amyloidosis + characteristic end organ damage

MGUS
<3 g M spike
<10% PC

AND

Smoldering MM
≥3 g M spike
or ≥10% PC

AND

Active MM
≥10% PC
≥3 g M spike

AND

Anemia, bone lesions, high calcium or abnormal kidney function

No anemia, bone lesions, normal calcium and kidney function

AL Amyloidosis

Kyle RA. NEJM 2002
Munshi N. IMWG 2011
Pathogenesis and presentation of AL amyloidosis


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**Systemic Amyloidosis**

- **Soft Tissue Involvement (22%)**
  - Periorbital Ecchymosis
  - Macroglossia
  - Pathognomonic: AL

- **Cardiac Involvement (45%)**
  - Heart Wall Thickening
  - Congestive heart failure
  - Constrictive cardiomyopathy

- **Renal Involvement (84%)**
  - Glomerulus deposition
  - Nephrotic range proteinurina
  - Peripheral Edema

- **GI Involvement (20%)**
  - Occult/Overt bleeding
  - Impaired motility
  - Hepatic infiltration
  - Malabsorption

- **Neuropathy (36%)**
  - Sensory (10%): Pain, Numbness, Tingling
  - Autonomic (26%): Orthostasis, Gastric dysmotility

- **Bleeding Diathesis (5%)**
  - Capillary fragility
  - Factor X deficiency

**Normal Kidney**

**Amyloid in glomerulus**

**Normal Liver**

**Amyloid in liver sinusoids**
Organ Involvement: Consensus Opinion

- **Objective criteria**
  - **Kidney**  > 500mg/day proteinuria
  - **Heart**  Mean wall thickness > 12 mm; (EKG; NT-Pro BNP, Troponin I, T)
  - **Liver/GI**  Liver span > 15 cm (absence of CHF); Alk phos > 1.5 x ULN
  - **PNS**  Orthostasis; symmetric sensorimotor neuropathy; impaired GI motility;

Staging: AL amyloidosis

- Retrospective review: Mayo Clinic
- 242 newly diagnosed patients
- Stored samples evaluated
  - Troponin I and T
  - NT-pro BNP

Biomarker threshold:
- Tn I: 0.1 μg/l
- NT-pro BNP: 332 pg/L

Cardiac disease is a critical cause of mortality in AL patients

Important for Selection of treatment

Serum Free Light Chain (FLC) assay

FLC assay in AL:
• A biomarker of disease (SPEP and UPEP often negative)
• Measure of response
• Predictor of disease status

Kumar et al. JCO 2012
Dispenzieri et al. Leukemia 2009.
Revised Staging System

- 758 patients
- Assigned points: 0-3
  - cTpnT ≥ 0.025 ng/mL
  - NT-Pro BNP ≥ 1800 pg/mL
  - FLC-diff ≥ 18 mg/dL
- Stage I-IV
  - Proportion patients/ Median OS
    - I: 189 (25%) / 94.1 months
    - II: 206 (27%) / 40.3 months
    - III: 186 (25%) / 14.0 months
      - IIIB: NT-Pro BNP > 8500/ 3 months
    - IV: 177 (23%) / 5.8 months
      (P<0.001)

Kumar et al. JCO 2012
Renal Amyloidosis

- Renal involvement occurs in 70-80% of AL
  - Significant morbidity; impacts treatment options
  - Less impact on OS compared to heart
  - Renal survival is impacted
- Factors to predict renal survival
  - Proteinuria
  - Estimated GFR
Renal Staging in AL

I: Proteinuria < 5g/24h \textbf{AND} eGFR > 50 mL/min
II: Either proteinuria > 5g/24 \textbf{OR} eGFR < 50 mL/min
III: Both proteinuria > 5g/24 h \textbf{AND} eGFR < 50 mL/min

Renal involvement and response matter!
Treatment of AL amyloidosis

• **Anti-plasma cell therapy**
  - Adapted from multiple myeloma
  - Caution: toxicity not trivial

• **Goals:**
  - Eradicate the pathologic plasma cell
  - Eliminate amyloidogenic free light chain
  - Prevent further amyloid deposition
  - Allow damaged organs to heal

• **Follow hematologic markers for response**
  - SFLC, SPEP, Quantitative immunoglobulins

• **Clinical trials**

**NO FDA APPROVED DRUGS AVAILABLE**
## Response Criteria

<table>
<thead>
<tr>
<th>Hematologic Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR)</td>
<td>Normal SFLC ratio with negative Serum and urine IFE</td>
</tr>
<tr>
<td>Very Good Partial Response (VGPR)</td>
<td>dFLC &lt; 4.0 mg/dL</td>
</tr>
<tr>
<td>PR</td>
<td>Reduction in dFLC &gt; 50%</td>
</tr>
<tr>
<td>No Response</td>
<td>&lt; 50% reduction in dFLC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organ Response*</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>NT-ProBNP response (&gt; 30% and &gt; 300 ng/L decrease in patients with baseline ≥ 650 ng/L) or NYHA response (≥ 2 class decrease in subjects with baseline NYHA class 3 or 4)</td>
</tr>
<tr>
<td>Kidney</td>
<td>50% decrease (at least 0.5 g/day) of 24 h urine protein (must be &gt; 0.5 g/day pretreatment) Creatinine and creatinine clearance must not worsen by 25% over baseline.</td>
</tr>
<tr>
<td>Liver</td>
<td>50% decrease in abnormal alkaline phosphatase. Decrease in liver size radiographically by at least 2 cm</td>
</tr>
<tr>
<td>PNS</td>
<td>Improvement in EMG nerve conduction velocity</td>
</tr>
</tbody>
</table>

*May take 3-12 months
**AL Treatment: Historical Perspective**

- **1971**: Fibrils = FLC
  - Case Studies MP
  - FLC Assay
    - Mdex Phase II (N=45)
- **1978**: MP Phase II (N=60)
  - MPC vs C Phase III
  - SCT Phase II (N=25)
- **1991**: MP vs MPC vs C Phase III (N=220)
  - Thalidomide Phase 1
  - 2005 Criteria
- **1996**: MP vs MPC Phase III (N=220)
  - 2005 Criteria
  - Thalidomide Phase 1
- **1997**: MPC vs C Phase III
  - Mdex vs SCT Phase III (N=100)
  - BNP Troponin
  - SCT + TD Phase II N=45
  - LenDex Phase II
- **1998**: MD+IFN (SWOG) Phase II
  - BNP Troponin
  - SCT + MP Phase II
- **2002**: DEXIFN
  - SCT + MP Phase II
  - BNP Troponin
- **2004**: Mdex vs SCT Phase III (N=100)
  - SCT + TD Phase II N=45
  - LenDex Phase II
- **2005**: 2005 Criteria
  - Thalidomide Phase 1
  - CPHPC + Anti SAP (mice)
  - LMD/MS
- **2007**: Ixazomib Phase I (N=100)
  - SCT + TD
  - LenDex Phase II
- **2009**: Bortez Phase I (N=70)
  - Anti-SAP Phase I
  - CPHPC + Anti SAP (mice)
  - LMD/MS
- **2011**: NEOD001 Phase I/II
  - Bortez Phase I (N=70)
  - Anti-SAP Phase I
  - CPHPC + Anti SAP (mice)
  - LMD/MS
- **2012**: NEOD Phases III
  - 2005 Criteria
  - Thalidomide Phase 1
  - CPHPC + Anti SAP (mice)
  - LMD/MS
- **2014**: Daratumumab
  - NT Pro-BNP Validated as a biomarker
  - CyBorD ± Dara
  - Ixazomib
  - CS1 expression
- **2015**: Anti-SAP Phase I
  - 11F4 Phase I
  - NEOD Phase III
  - Revised Mayo Staging
  - 2005 Criteria
  - Thalidomide Phase 1
  - CPHPC + Anti SAP (mice)
  - LMD/MS
- **2016**: Daratumumab
  - NT Pro-BNP Validated as a biomarker
  - CyBorD ± Dara
  - Ixazomib
  - CS1 expression
- **2017**: Daratumumab
  - NT Pro-BNP Validated as a biomarker
  - CyBorD ± Dara
  - Ixazomib
  - CS1 expression
Transplant or not to Transplant

Transplant Eligibility
- Physiologic Age ≤ 70
- ECOG Performance Score ≤ 2
- CrCl ≥ 30 ml/min* (unless on chronic dialysis)
- NYHA Class I/II

Transplant Ineligibility
- TnT ≥ 0.06 ng/ml
- NT-proBNP ≥ 5000
- More than 2 organs † significantly involved
- Poor integrity of GI mucosa

*Selected patients may become eligible for PBSCT with renal transplantation
† Organs considered for this criteria include liver, heart, kidney or autonomic nerve

Adapted: Mayo Clinic Msmart criteria: 2013
HDM / ASCT: Boston Experience

- 629 patients with AL amyloidosis underwent HDM/SCT 1994 – 2014
- Patient Characteristics
  - Median age 57 years (28-80)
  - Organ involvement
    - Cardiac 53%
    - ≥ 2 organ system 41%
- Conditioning regimens
  - Mel 200: 350 (55.6%)
  - Mel 100-140: 279 (44.3%)
- TRM: 7.4%: 47/629
  - 3.4% (10/292) since 2005

Sanchoawala et al. Blood, November 2015
HDM / ASCT: Boston Experience

Response Rate
- Hematologic CR at 6-12 months: 40.3%
  - Intention to treat: 34.8%
  - Mel 200 mg/m2: 44.9%
  - Mel 100-140: 33.8%
    * (p= 0.009)

Relapse from CR
- 40 patients (18.2%) relapsed at a median of 3.97 years
  - 24 received Mel 200
  - 16 received Mel 100-140
Hematologic Response: Critical

Overall Survival
Hematologic CR vs Non-CR

Hem-CR
Median OS not reached

Hem non-CR
Median OS 6.3 yrs

\( P < 0.0001 \)
Summary: High Dose Melphalan/ASCT

- Effective treatment approach for selected patients
  - Cardiac disease predicts survival
- Rapid suppression of light chain production
  - Suspends amyloid production
  - Arrests disease progression
  - Allows for organ improvement
    - Renal, cardiac, hepatic and quality of life
    - Extends survival
- TRM can be mitigated at experienced centers

Goal: Hematologic CR
## Transplant Approaches To Increase CR

<table>
<thead>
<tr>
<th>Approach</th>
<th>Number of Patients</th>
<th>Hematologic Response</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCT &amp; Thal/dex consolidation (Cohen et al. 2007)</td>
<td>45 total 31 TD</td>
<td>21% CR 39% CR (1 yr)</td>
<td>84% (2 yr OS) TRM 4.4%</td>
</tr>
<tr>
<td>ASCT &amp; BD consolidation (Landau et al. 2011)</td>
<td>40 total 23 BD</td>
<td>27% CR 58% CR (1 yr)</td>
<td>82% (2 yr OS) TRM 10%</td>
</tr>
<tr>
<td>Bor/Mel Conditioning (Sanchorawala et al. 2011)</td>
<td>10 (pilot study)</td>
<td>RR: 80% CR: 67%</td>
<td>100% (23 months)</td>
</tr>
<tr>
<td>BD induction + ASCT vs. ASCT (Huang et al. 2014)</td>
<td>56 28 each arm</td>
<td>BD +ASCT: 85.7% (1 yr) CR: 70% (2 yr) ASCT: 53.5% (1 yr) CR: 35% (2 yr)</td>
<td>BD + ASCT: 95% (2 yr) ASCT: 69.4% (2 yr)</td>
</tr>
<tr>
<td>Bor induction &amp; Bor/Mel conditioning (Sanchorawala et al. 2015)</td>
<td>35 (30 went on to SCT)</td>
<td>100% (assessable pts) 77% (ITT) 63% CR 37% VGPR</td>
<td>TRM: 8.5% Median PFS and OS not reached @ 36 months</td>
</tr>
</tbody>
</table>
Multicenter- RCT (29 centers in France)
► Newly diagnosed AL amyloidosis
► Ages 18-70 years
► ECOG ≤ 2

Two arm study:
Arm A: Oral melphalan (10mg/m²) + Dex (40mg), both days 1-4, monthly
Arm B: High Dose Melphalan (140 – 200mg/m²) + SCT

Jaccard A. et al. NEJM 2007
High dose melphalan + SCT versus oral melphalan + dexamethasone

37 patients: HDM/SCT
10: MEL 140mg/m2
>65y
EF~30%
CrCl<30ml/m
AP>5x nml

27: MEL 200 mg/m2

9/37 died within first 100 days
TRM: 24%

Transplants performed at different 29 centers

Jaccard A. et al. NEJM 2007
Survival By Response & Treatment

Heme Response rates:
- Mel-Dex: 67%; CR: 61%
- HDM/SCT: 68%; CR: 47%

Median Survival:
- Mel/Dex: 56.9 months
- HDM/SCT: 22.2 months
(P = 0.04)

Median follow up:
- Whole cohort: 24 months
- Survivors: 36 months

Jaccard A et al. NEJM 2007
Letters to the editor:

TO THE EDITOR: The French phase 3 trial of stem-cell transplantation for systemic AL amyloidosis shows the morbidity that results when the treatment of patients with multiorgan dysfunction is based on criteria for transplantation that are “not as stringent as those used in large North American centers.”\(^1\,^{2}\) We have completed a phase 2 trial testing risk-adapted stem-cell transplantation and adjuvant chemotherapy in 45 patients with newly diagnosed, untreated AL amyloidosis (NCT000089167). Aggressive supportive measures minimized the morbidity associated with granulocyte colony-stimulating factor and gastrointestinal bleeding, and there was a stopping rule for a rate of treatment-related morbidity exceeding 10%. The rate of treatment-related morbidity was 4%; the rates of overall and complete hematologic responses were 79% and 38%, respectively; and the rate of organ responses was 48%.\(^3\) Median survival is undefined and for patients with cardiac involvement exceeds 3 years. Raymond L. Comenzo, M.D. Richard M. Steingart, M.D. Adam D. Cohen, M.D. Memorial Sloan-Kettering Cancer Center

TO THE EDITOR: The French multicenter study reported by Jaccard et al. showed no difference between high-dose melphalan and melphalan plus dexamethasone in AL amyloidosis. This finding raises questions concerning the management of life-threatening diseases. Should patients with rare diseases such as amyloidosis be treated anywhere (the average center enrolled <1 patient annually) or only at experienced referral centers?\(^1\) Does the need for simple treatment options that can be delivered anywhere and to everyone negate the need to develop intensive (and potentially toxic) options that may provide additional therapeutic benefit for selected patients? Transplant-related mortality is substantially higher at low-volume, inexperienced centers\(^2\) — very likely a concern with most of the study centers.

It is unclear whether the groups in the French study were truly comparable, since no information was provided on levels of the N-terminal fragment of B-type natriuretic peptide and troponin T, biomarkers shown to be of critical prognostic significance in amyloidosis.\(^2\) Jayesh Mehta, M.D. Robert H. Lurie Comprehensive Cancer Center

TO THE EDITOR: The inferior survival (median, 22 months) of patients treated with high-dose melphalan for AL amyloidosis, as reported by Jaccard et al., is probably due to the design of the study. Intensive treatment of AL amyloidosis is a challenge; in the French trial, there were 50 intended transplantations during 5 years in 29 centers, and treatment delay may have contributed to the high treatment-related mortality in the high-dose melphalan group.

In the prospective multicenter trial conducted by the Dutch–Belgian Hemato-Oncology Cooperative Group (HOVON), 70 previously untreated patients with AL amyloidosis (World Health Organization performance-status score, 0 to 2), 47% of whom had cardiac involvement and more than 55% of whom had high-risk disease,\(^4\) received vin-cristine, doxorubicin, and dexamethasone (VAD), followed in 47 patients by high-dose melphalan (140 to 200 mg per square meter). The transplantations were performed in tertiary referral centers. Nine patients died from treatment-related causes (13%): seven during treatment with VAD and two after treatment with high-dose melphalan. The 4-year overall survival rate among all the patients was 62%, while the 4-year survival rate after transplantation was 78%.

We believe that there is still insufficient evidence that intensive therapy for AL amyloidosis should be abandoned.

Henk M. Lokhorst, M.D., Ph.D.

• Study included poor patient selection for SCT
• Transplants performed at centers with little experience → ↑TRM
• SCT should not be abandoned and remain standard in U.S.A.
Transplant ineligible patients: Off Trial

- Melphalan + Dexamethasone
- Dose: Mel 0.22 mg/kg + Dex 40mg D 1-4/28
  - Hematologic response rate of 67%, 33% CR
  - Organ responses 48%
  - Median OS 5.1 years
  - PFS: 3.85 years
  

– Further validated in comparison to transplant
  
<table>
<thead>
<tr>
<th>Regimen (Ref)</th>
<th>Study Type</th>
<th>Population</th>
<th>N (total/evaluable)</th>
<th>Heme RR% (CR)</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bor (Reece et al. Blood 2011)</td>
<td>phase I/II</td>
<td>relapsed</td>
<td>70</td>
<td>QW 69 (38) BIW 67 (24)</td>
<td>QW 94% (1 yr OS) TW: 84% (1 yr OS)</td>
</tr>
<tr>
<td>BorDex (Kastritis et al. J Clin Oncol. 2010)</td>
<td>series</td>
<td>new (19%), relapsed (81%)</td>
<td>94/93</td>
<td>72 (25)</td>
<td>76% (1 yr OS)</td>
</tr>
<tr>
<td>Mdex vs. BorMDex Kastritis et al. ASH abstract 2014</td>
<td>Randomized Phase III</td>
<td>new</td>
<td>35 Mdex 35 Bortex MDEX</td>
<td>58 76</td>
<td>Not reported</td>
</tr>
<tr>
<td>BorMDex Gasparetto et al. ASCO abstract 2010</td>
<td>phase II</td>
<td>new and relapsed</td>
<td>30/29</td>
<td>83 (45)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Cy/Bor/Dex Venner et al. Blood 2012</td>
<td>Retrospective series</td>
<td>new and relapsed</td>
<td>43</td>
<td>81.4 (41.9)</td>
<td>97% (2 year OS)</td>
</tr>
<tr>
<td>Cy/Bor/Dex Mikhael et al. Blood 2012</td>
<td>Retrospective series</td>
<td>new and relapsed</td>
<td>17</td>
<td>94 (71)</td>
<td>71% (median f/u 21 months)</td>
</tr>
</tbody>
</table>
**Next Generation Proteosome Inhibitors**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
<th>Response</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib Phase I/II</td>
<td>N=28</td>
<td><strong>Heme Responses:</strong> ORR = 63%</td>
<td>Median PFS: 20 months</td>
<td>MTD 20/36</td>
</tr>
<tr>
<td>(Cohen et al. ASH 2016)</td>
<td></td>
<td>6/8 PI-refractory patients</td>
<td></td>
<td>Fatigue: most common AE</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dex added in 5 pts→3 response upgrades</td>
<td></td>
<td>10 Grade 3/4 cardiopulmonary toxicities</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Organ Responses</strong></td>
<td>Median OS: Not reached</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (21%) (3 kidney, 1 GI, 1 liver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ixazomib Phase I/II</td>
<td>N=27</td>
<td>Heme Responses ORR= 52%</td>
<td>1-year PFS: 60%</td>
<td>MTD: 4mg days 1,8,15 of 28</td>
</tr>
<tr>
<td>(Sanchorawala et al. Blood, 2017)</td>
<td></td>
<td>PFS: 14.8 months</td>
<td>1-year OS: 85%</td>
<td>Grade 3 AE: Dyspnea, fatigue, Subcutaneous</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Organ Responses 56% (5 renal,5 cardiac)</td>
<td></td>
<td>tissue disorder</td>
</tr>
</tbody>
</table>
## Immunomodulatory Agents

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Number of Patients</th>
<th>Hematologic response % (CR%)</th>
<th>Overall Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thal/Dex</td>
<td>31</td>
<td>48(19)</td>
<td>Not specified (60% grade 3 toxicity)</td>
</tr>
<tr>
<td>Palladini et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Len/Dex</td>
<td>34</td>
<td>67(29)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Sanchorawala et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Len/Dex</td>
<td>23</td>
<td>41</td>
<td>Not specified</td>
</tr>
<tr>
<td>Dispenzieri et al.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclo/Len/Dex</td>
<td>35</td>
<td>60 (11)</td>
<td>37.8 months</td>
</tr>
<tr>
<td>Kumar et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mel/Len/Dex</td>
<td>26</td>
<td>58</td>
<td>80.8% at 2 years</td>
</tr>
<tr>
<td>Moreau et al</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Pom/Dex</td>
<td>33</td>
<td>48 (3)</td>
<td>76% at 1year</td>
</tr>
<tr>
<td>Dispenzieri et al.</td>
<td></td>
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</tbody>
</table>
Immunotherapy: Daratumumab

- Fully human IgG kappa mAb targeting CD38
- Approved for MM
  - Combination therapy after 1 prior line
  - Monotherapy after 3 lines

Phase II Study: Safety and Tolerability of Daratumumab in Patients With Relapsed AL

Preliminary results: Dr. Sanchorawala ASH 2017
Daratumumab: Adverse Events

• No grade 3-4 infusion related reactions
• First 2 patients experience grade 1 nausea and vomiting with first infusion, resolved with antiemetics
  – No additional patients experienced N/V after introduction or pre-infusion ondansetron
  – No hospitalizations for infusion related or other adverse events.
Daratumumab: Hematologic Response

12 patients with relapsed AL > 1 prior line were treated

- Percent reduction in dFLC after 1 infusion
  - 3 months (9 evaluable patients): 2CR, 6VGPR, 1PR
  - 6 months (4 evaluable patients): 2CR, 2VGPR

Involved FLC levels pre and post 1 infusion

SanchoRAWala et al. ASH 2017
Daratumumab Organ Responses

• Cardiac Response
  – >30% reduction in NT-proBNP
    – 1 month: 8% (n=1/12)
    – 3 months: 33% (n=3/9)
    – 6 months: 75% (n=3/4)

• Renal Response
  – >30% reduction in urine protein excretion
    – 1 month: 17% (n=1/6)
    – 3 months: 56% (n=5/9)
    – 6 months: 80% (n=4/5)

Sanchorawala et al. ASH 2017
Management for Relapsed Disease

Relapsed/Refractory AL Amyloidosis

- Daratumumab Based Treatment
  - PI Sensitive
    - CyBorD
    - VD
    - Carfilzomib
    - Ixazomib
  - PI Refractory
    - Len/Dex
    - Pom/Dex

Clinical Trials
Supportive Measures

• Critical in caring for this complicated population
  – Cautious use of cardiac meds
    • Hypotension in setting of autonomic neuropathy
  – Close fluid management
    • Diuretics, albumin, compression hose
  – Attention to bleeding and factor X level
    • Factor IX complex, factor VIIa, PTCC
  – Neuropathy management
    • midodrine, gabapentin, pregabalin, duloxetine, metaclopramide
  – Nutritional support
Investigational Approaches

- CyBorD ± Daratumumab upfront
  - Phase III: study open for enrollment
- Elotuzumab: Anti-CS1 monoclonal antibody
  - Phase II Study: Elotuzumab, Lenalidomide and Dex +/- Cyclophosphamide
- Venetoclax: BCL-2 inhibitor
- Cellular therapies:
  - CAR-T
Anti-Amyloid Therapies in AL

• Protein Stabilizers
  – Doxycycline
    • Reduces fibril formation invitro
      – (Ward et al. NEJM 2011)
    • Improved outcomes clinically
      – Mayo Clinic, London Amyloid group

• Monoclonal Antibodies
  – Anti-SAP
  – 11-aF4
  – NEOD001
Amyloid protein focused treatment: Doxycycline

Doxycycline

• Can reduce fibril formation in vitro and in vivo

• Mayo Clinic Experience
  – 455 AL Rx ASCT 1996-2011
  – 106 (23%) received doxycycline post transplant
    • pen allergic

Overall Survival

Median OS: 161 months entire cohort
Doxycycline: Not reached
Others: 113 months
(P = 0.09)

Kumar et al. ASH abstracts 2012
**Doxycycline: Improved Outcomes Early**

**Case series  ASH 2015**

- AL with cardiac involvement
  - 30: received doxycycline
    - 100 mg BID
  - 73 matched controls
    - Mayo stage II/III
- Heme Response w/chemo
  - 72% bortex, 23% thal, 5% Mel
  - Overall %CR/VGPR/PR:
    - 33/9/29
    - Doxy: 56/10/30
    - Non doxy: 35/8/37

**Doxycycline with chemotherapy:**
Significantly improved CR/VGPR & OS for stage II/IIIa

Wechalekar et al. ASH abstract 2015
NEOD001: Anti-Amyloid Antibody

- IgG1 humanized antibody against cryptic epitope on misfolded light chain
- NEOD001 Phase 1/2 Trial
  - 27 Patients with AL amyloidosis and prior chemotherapy
    - Off Anti-plasma cell therapy at time of enrollment
    - At least renal or cardiac involvement
    - Very advanced organ involvement excluded

Gertz et al. JCO  Feb 8, 2016
NEOD001 Mechanism of Action – 2A4 Induces Phagocytosis of Aggregated Light Chain Amyloid (AL)

Isotype control mAb

2A4: murine form of NEOD001
NEOD001 Phase 1/2 Clinical Trial

• Primary Objective: Safety and tolerability
  • Well tolerated: 24 mg/Kg monthly
  • No treatment-emergent adverse events (TEAE) of grade 3 or higher reported; no serious TEAEs

• Expansion Cohort of 42 Additional patients enrolled at 24 mg/kg/month
  – Secondary Objectives
    • Organ responses: Cardiac, Renal, PNS
      – NT-ProBNP, Proteinuria, NIS-LL
Total cardiac evaluable (n = 36)

19 responders (53%)
17 stable (47%)

Median time to initial response: 2 months

Evaluable patients had baseline NT-proBNP ≥650 pg/mL without progressive renal dysfunction1,2

- **Response:** >30% and >300 pg/mL decrease in NT-proBNP
- **Progression:** >30% and >300 pg/mL increase in NT-proBNP
- **Stable disease:** Neither response nor progression

*30% decline, 453 pg/mL reduction from baseline. † 42% decline, 271 pg/mL reduction from baseline.
Total renal evaluable (n = 36)

23 responders (64%)
13 stable (36%)

• **Response**: >30% decrease in proteinuria or a decrease to <0.5 g/24 hours in the absence of renal progression
• **Progression**: >25% worsening in eGFR
• **Stable disease**: Neither response nor progression

Median time to initial response: 4 months

Evaluable patients had baseline proteinuria >0.5 g/24 hours
Peripheral Neuropathy Expansion Cohort (N = 11)

9 responders (82%)
2 progressors (18%)

Neuropathy responders: <2-point increase in NIS-LL from baseline; response criteria established in patients with diabetic nephropathy and in use in clinical trials for diabetic neuropathy and TTR polyneuropathy.

*Patient discontinued at month 4, last observation carried forward for 2 patients not having NIS-LL at month 10.
NEOD001: Recent Trials

• Pronto:
  – Phase 2b, randomized double blind, placebo controlled study of NEOD001 in previously treated AL
    • Persistent cardiac dysfunction
    • Without need for further anti-plasma cell treatment

• Vital:
  – Phase 3, randomized, double blind, placebo controlled study of standard of care chemotherapy with or without NEOD001
    • Newly diagnosed patients with AL
    • Cardiac involvement
11-1F4: Anti-Amyloid Monoclonal Antibody

- 11-F4 mAb (CAEL-101)
  - Developed to target exposed epitope following fibrillogenesis

Kappa Bence Jones protein isolated and used to develop Ab

Native

Structure of soluble light chain in circulation → not reactive with 11-1F4 mAb (CAEL-101)

“Loop-Flip”

Structure of light chain in fibril → reactive with 11-1F4 mAb (CAEL-101)

- Fibrillogenesis
- Surface adsorption
Phase 1a/b study of 11-1F4

- Study: Open-label, dose escalation study
  - Confirmed diagnosis of AL
  - Received prior systemic therapy
  - Not requiring anti-plasma cell therapy
- Objectives:
  - Determine maximum tolerated dose
  - Demonstrate reduction in amyloid burden by decrease of organomegaly and/or improved organ function
Phase 1a/b study of 11-1F4

- 27 patients enrolled; 24 evaluable for response
  - No Dose limiting toxicity up to an MTD of 500 mg/m²
- Best Cardiac Response:

  - PROGRESSION
    - >30% and >300 pg/ml increase in NT-proBNP
  - STABLE
    - Baseline NT-proBNP ≥650 pg/ml
  - RESPONSE
    - >30% and >300 pg/ml decrease in NT-proBNP

  12 patients evaluable for response
  8 responders – 67%  
  4 stable

Median time to cardiac response - 3 weeks
Phase 1a/b study of 11-1F4

- Best Renal Response:

Percent change in baseline 24 hour Urine Protein (%)

- Median time to renal response – 4 weeks*
  *24 hour urine protein measured at screening and Week 8 in Phase 1a and at screening and Weeks 5, 8 and 12 in Phase 1b
Organ responses independent of chemotherapy

- Patient with cardiac Lambda AL Amyloidosis
- 6 prior treatments with best Hematologic Response PR
- Prior to 11-1F4 mAb (CAEL-101) NO Organ response

graph showing NT-proBNP (pg/mL) over time with various treatments and responses:
- Mel-Dex: NO RESPONSE
- Ninlaro-Dex: NO RESPONSE
- Cytoxan-Ninlaro-Dex: NO RESPONSE
- Len-Ixazomib: PARTIAL RESPONSE
- Dara-Len-Dex: NOT TOLERATED
- Dara-Pom-Dex: STABLE DISEASE
- Organ Response after 3 weeks of 11-1F4
Summary

► Recognition of the signs and symptoms is critical for early diagnosis and improved outcomes
► Disease assessment requires: amyloid subtyping, FLC testing and cardiac biomarker staging
► Goal of therapy: eradicate the pathologic light chain
► High dose melphalan + SCT still standard for now
► Novel agents and approaches are evolving!
► Doxycycline may help stabilize light chains
► Amyloid directed therapy results are encouraging
► Supportive measures essential
Acknowledgments:

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Thank you!

Contact information
Email: mrosenzweig@coh.org
Phone: 626-256-4673 ext: 82405