Light Chain (AL) Amyloidosis Diagnosis & Management

Michael Rosenzweig, MD
How The Experts Treat Hematologic Malignancies
March 16, 2017
Disclosures

• Speakers Bureau:
  – Celgene
  – Bristol-Myers Squibb
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: Background

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

Protein Misfolding and Congo Red Stain

## 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 Mutated TTR (familial)</td>
<td>Mutant TTR</td>
<td>Peripheral/autonomic neuropathy, CMY, vitreous opacities</td>
</tr>
<tr>
<td>Wild-type (senile)</td>
<td>Normal TTR</td>
<td>Restrictive CMY; carpel tunnel syndrome</td>
</tr>
<tr>
<td>LECT2</td>
<td>Leukocyte chemotactic factor 2</td>
<td>Renal (acquired)</td>
</tr>
<tr>
<td>Aβ₂M</td>
<td>B₂-microglobulin</td>
<td>Carpel Tunnel, arthropathy</td>
</tr>
<tr>
<td>Other Hereditary Afib Alys ApoA1 Agel</td>
<td>Fibrinogen alpha Lysozyme A-1 Apolipoprotein Gelsolin</td>
<td>Renal Renal (most common) Renal (most common Cranial neuropathy</td>
</tr>
</tbody>
</table>
The Amyloid Expert Has Many Roles

- Detective: Diagnostic challenge
- Warrior: Destroy the plasma cell clone
- Contractor: Demolish the amyloid
- Caregiver: Manage the complications

- One (and only one) character emulates the genius and versatility required:

Snoopy of course
Diagnosing Amyloidosis: The Detective

Diagnostic Challenge of Amyloidosis:
Symptoms are non-specific and mimic other diseases
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

- Must think it to diagnose it!
- Early diagnosis is critical
  - Many diseases mimic amyloidosis
- 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
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

Vrana et al. Blood 2009

<table>
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<tr>
<th># Accession</th>
<th>MW</th>
<th>Control</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</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>
<td>100% (35)</td>
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<tr>
<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% (13)</td>
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<td>12 kDa</td>
<td>100% (7)</td>
<td>100% (8)</td>
<td>100% (7)</td>
<td>100% (8)</td>
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<tr>
<td>5 APOA4_HUMAN</td>
<td>45 kDa</td>
<td>100% (15)</td>
<td>100% (19)</td>
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<tr>
<td>6 SAMP_HUMAN</td>
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<td>100% (8)</td>
<td>100% (9)</td>
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<tr>
<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>9 CLUS_HUMAN</td>
<td>52 kDa</td>
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<td>100% (7)</td>
<td>100% (8)</td>
<td>100% (8)</td>
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<tr>
<td>10 CO6A3_HUMAN</td>
<td>344 kDa</td>
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<td>100% (5)</td>
<td>100% (9)</td>
<td>100% (7)</td>
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<td>100% (7)</td>
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<td>13 TRFE_HUMAN</td>
<td>77 kDa</td>
<td>100% (7)</td>
<td>100% (6)</td>
<td>100% (9)</td>
<td>100% (4)</td>
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<td>15 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>
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</tbody>
</table>
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
AL: Monoclonal Gammopathy 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

AL Amyloidosis + characteristic end organ damage

MGUS
- <3 g M spike
- <10% PC

Smoldering MM
- ≥3 g M spike
- or ≥10% PC

Active MM
- ≥10% PC
- ≥3 g M spike
- AND

No anemia, bone lesions, normal calcium and kidney function

Anemia, bone lesions, high calcium or abnormal kidney function

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


©2014 by Ferrata Storti Foundation
**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 proteinuria
- Peripheral Edema

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

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

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

<table>
<thead>
<tr>
<th>Stage</th>
<th>n</th>
<th>Deaths</th>
<th>MS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I-i</td>
<td>59</td>
<td>48</td>
<td>27.2</td>
</tr>
<tr>
<td>Stage II-i</td>
<td>91</td>
<td>85</td>
<td>11.1</td>
</tr>
<tr>
<td>Stage III-i</td>
<td>92</td>
<td>89</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Serum Free Light Chain (FLC) assay

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

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 Overall Survival
    - I: 189 (25%) / 94.1 months
    - II: 206 (27%) / 40.3 months
    - III: 186 (25%) / 14.0 months
    - IV: 177 (23%) / 5.8 months
      (P<0.001)

Kumar et al. JCO 2012
Treatment of AL: Attacking the Plasma Cells

The Warrior
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

### Hematologic Response

<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>

### Organ Response*

<table>
<thead>
<tr>
<th>Organ</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

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*Image credits to City of Hope.*
AL Treatment: Historical Perspective

**1971**
- Fibrils= FLC

**1991**
- MP vs MPC vs C Phase III (N=220)

**1997**
- MP vs MPC vs C Phase III (N=220)
- Case Studies MP

**2002**
- MP vs MPC vs C Phase III (N=220)

**2005**
- 2005 Criteria Thalidomide Phase 1
- FLC Assay
  - Mdex Phase II (N=45)

**2009**
- 2005 Criteria Thalidomide Phase 1
- CPHPC + Anti SAP (mice)
- LMD/MS

**2012**
- CyBorD Clinical Research Guidelines
- SCT + BD Revised Mayo Staging

**2015**
- Anti-SAP Phase I
- 11F4 Phase I
- NEOD Phase III

**2016**
- Daratumumab Case Report
- NT Pro-BNP Validated as a biomarker

**1978**
- MP Phase II (N=60)

**1996**
- MPC vs C Phase III

**1998**
- SCT Phase II (N=25)
- SCT + MP Phase II
- BNP Troponin

**2004**
- SCT + TD Phase II N=45
- LenDex Phase II

**2007**
- Bortez Phase I (N=70)
- Mdex vs SCT Phase III (N=100)

**2011**
- Ixazomib Phase III
- Carfilzomib Phase I/II

**2014**
- SCT + TD Phase II N=45
- LenDex Phase II
- Bortez Phase I (N=70)

**2016**
- Daratumumab Case Report
- NT Pro-BNP Validated as a biomarker

**1971**
- 1978
- 1996
- 1998
- 2004
- 2007
- 2011
- 2014
- 2016
Treatment Algorithm

Newly diagnosed AL amyloidosis

- Transplant eligible
  - BM PC ≥ 10% or CRAB
  - Yes: Induction 2-4 cycles
  - No: Mel 200 HSCT

- Not wanting transplant

- Transplant ineligible
  - Mel-Dex or CyBorD
  - ≥ Hematologic VGPR

Msmart guidelines
Mayo Clin Proc 2015
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

Sanchorawala 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
HDM / ASCT: Boston Experience

Overall Survival with HDM/SCT 1994-2014

Median OS: 7.63 years

Long term survival > 20 years: 29%
How Far We Have Come!

Melphalan, Prednisone and Colchicine (MPC) vs. Colchicine (C)

Overall Survival

Median Overall Survival:

All patients: 8.4 months
MPC: 12.2 months
C: 6.7 months

**Hematologic Response: Critical**

**Overall Survival**
Hematologic CR vs Non-CR

![Graph showing overall survival](image)

- **Hem-CR**
  - Median OS: not reached
  - *p* < 0.0001

- **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

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 (Sanchoorawala 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% (1yr) 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 (Sanchoorawala 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%

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

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

P = 0.04

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.” 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 (NCT00089167). 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 36%, respectively; and the rate of organ responses was 48%. 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 Jacqard 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? 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 — 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.

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 Jacqard 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 transplant-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, received vincristine, 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.
Treatment Algorithm

Newly diagnosed AL amyloidosis

Transplant eligible

- BM PC ≥ 10% or CRAB
  - Yes: Induction 2-4 cycles
    - No: Mel 200 HSCT

- Not wanting transplant
  - Mel-Dex or CyBORd

Transplant ineligible

- ≥ Hematologic VGPR

Clinical Trial

Msmart guidelines 2014
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

## Novel Agents: Bortezomib

<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>
## Novel Agents: 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>
<td></td>
</tr>
<tr>
<td>Pom/Dex</td>
<td>33</td>
<td>48 (3)</td>
<td>76% at 1 year</td>
</tr>
<tr>
<td>Dispenzieri et al.</td>
<td></td>
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</tbody>
</table>
## Recent Studies

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Patients</th>
<th>Response</th>
<th>Survival</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Carfilzomib Phase I/II (Cohen et al. ASH 2016) | N=28     | **Heme Responses:** ORR = 63%  
6/8 PI-refractory patients  
Dex added in 5 pts→3 response upgrades  
**Organ Responses:** 5 (21%) (3 kidney, 1 GI, 1 liver) | Median PFS: 20 months  
Median OS: Not reached | MTD 20/36  
Fatigue: most common AE  
10 Grade 3/4 cardiopulmonary toxicities |
| Daratumumab Case Report (Sher et al. Blood 2016) | N= 2 MM/AL Heavily pre-treated | **Heme Response:**  
Pt 1: CR after 8 weekly treatments  
Pt 2: CR x 12 weeks  
**Organ Response:** Too early | 100% | Heavily Pre-treated:  
SCT; Bor; Imid; Dex; Carfilzomib |
Management of AL Patients: Supportive Care

The Caregiver
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
**Treatment Algorithm**

Newly diagnosed AL amyloidosis

- **Transplant eligible**
  - BM PC $\geq 10\%$ or CRAB
    - **Yes**
      - Induction 2-4 cycles
        - **Yes**
          - Mel 200 HSCT
        - **No**
          - Observation
  - **No**
    - Not wanting transplant
      - **Mel-Dex or CyBorD**

- **Transplant ineligible**
  - $\geq$ Hematologic VGPR
    - **Yes**
      - $\geq$ PR
        - **Yes**
          - More chemotherapy
        - **No**
          - More chemotherapy
    - **No**
      - More chemotherapy

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Msmart guidelines
Mayo Clin Proc 2015

Clinical Trial
mSMART: Off Trial

Key area for clinical trials

Msmart guidelines
Mayo Clin Proc 2015
Anti-Amyloid Treatment: Demolishing Amyloid!

The Contractor
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
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

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/IIla

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)
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
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    - At least renal or cardiac involvement
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Gertz et al. JCO  Feb 8, 2016
NEOD001 Phase 1/2 Clinical Trial

- **Primary Objective:** Evaluate safety and tolerability of NEOD001
  - Determine Phase 2 dosing
    - Well tolerated: 24 mg/Kg monthly
    - No treatment-emergent adverse events (TEAE) of grade 3 or higher reported; no serious TEAEs
    - Most common AE: Fatigue; URI:

- Expansion Cohort of 42 Additional patients enrolled at 24 mg/kg/month
  - **Secondary Objectives**
    - Organ responses: Cardiac, Renal, PNS
      - NT-ProBNP, Proteinuria, NIS-LL

Gertz et al. JCO  Feb 8, 2016
NEOD001: Cardiac Biomarker Response
Best Response Analysis

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 dysfunction\(^1,2\)
- **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. \(^\dagger42\%\) decline, 271 pg/mL reduction from baseline.
NEOD001 Cardiac Responses Continue to Deepen for 36 Months

47-Year-Old Man

Previous treatment: CyBorD
Baseline NT-proBNP: 3312 pg/mL

Best NT-proBNP: 513 pg/mL (~85%)

Safety: 1 grade 3 SAE (chest pain), not related; no dose interruptions

Clinical outcome: Progressive functional improvement; edema significantly improved with reduction in diuretic needs

Includes 3 time points from OLE
NEOD001: Renal Biomarker Response
Best Response Analysis

Total renal evaluable (n = 36)
23 responders (64%)
13 stable (36%)

Median time to initial response: 4 months

- **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

Proteinuria % Change From Baseline

- eGFR, estimated glomerular filtration rate.
- Evaluable patients had baseline proteinuria >0.5 g/24 hours
NEOD001 Renal Responses Continues to Deepen for 30 Months

61-Year-Old Man

Previous treatment: LDex then Bor-LDex then HDM/ASCT

Baseline proteinuria (24 hours): 5129 mg/d

Best proteinuria (24 hours): 294 mg/d (−94%)

Safety: No SAEs; no grade ≥3 AEs; no dose interruptions

Clinical outcome: Progressive functional improvement; edema completely resolved; patient no longer has fatigue

ASCT, autologous stem cell transplantation; Bor-LDex, bortezomib, lenalidomide, dexamethasone; HDM, high-dose melphalan; LDex, lenalidomide, dexamethasone.
Peripheral Neuropathy Expansion Cohort (N = 11)

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

Complete 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: Subgroup Analysis

• NEOD001 organ responses are not related to
  – *Time* since best or last HR
  – *Depth* of best or last HR
  – PCD therapy within previous 6 months or 12 months
  – *Type* of last PCD therapy
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
Summary

- Recognition of the signs and symptoms can result in early diagnosis and improved outcomes
- Disease assessment requires: amyloid subtyping, FLC testing and cardiac biomarker staging
- Goal of therapy: eradicate the pathologic light chain
- Supportive measures essential
- High dose melphalan + SCT still standard
- Novel agents and approaches are useful
- Amyloid directed therapy available on clinical trial
Acknowledgments:

- Amyloidosis Foundation:
  - David Seldin Memorial Research Award
- The Judy and Bernard Brisken Center for Multiple Myeloma (plasma cell disease) Research at City of Hope
Thank you!

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