LIGHT CHAIN (AL) AMYLOIDOSIS
DIAGNOSIS & MANAGEMENT

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How the Experts Treat Hematologic Malignancies
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Disclosures

M. Rosenzweig
• Speakers Bureau:
  – Celgene
  – Bristol-Myers Squibb

J. Bautista
• None
Amyloidosis: Lecture Outline

- Definition & diagnosis
  - when to suspect and how to confirm
- Classification: subtype impacts treatment
- Staging
- Amyloid related organ disease
- 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 of proteins known to form amyloid

Protein Misfolding and Congo Red Stain

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 of monoclonal gammopathy

**Diagnostic Challenge of Amyloidosis:**
Symptoms are non-specific and mimic other diseases
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 diagnose 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 7-10 cm 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 10 ml 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

Gross tissue

Congo red stain

Apple green birefringence

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
  - Cannot assume AL!

Amyloid Subtype: Must be known!
AL Amyloidosis: Light Chain Amyloidosis

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

AND

Anemia, bone lesions, high calcium or abnormal kidney function

Kyle RA. NEJM 2002
Munshi N. IMWG 2011
Pathogenesis and Presentation of AL Amyloidosis

underlying clone → excess production of unstable FLC → misfolded light chains allowing exposure of hidden epitopes which allow aggregation → pre-fibrillar aggregates → amyloid fibrils formation in an ordered β-pleated sheet structure in tissues → organ damage due to fibril deposition → direct tissue toxicity (mainly affecting the heart)

renal 11%  periorbital purpura 14%  macroglossia 13%

Systemic Amyloidosis

Soft Tissue Involvement (22%)
- Periorbital ecchymosism
- 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

Normal Kidney
Amyloid in glomerulus
Normal Liver
Amyloid in liver sinusoids
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

Stage I-i: both < threshold
Stage II-i: either ≥ threshold
Stage III-i: both ≥ threshold

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 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
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
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
• NYHA Class III/IV
• 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’s 20-year 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
- Complete heme response rate
  - 40.3% at 6-12 months

Sanchorawala et al. Blood, November 2015
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

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
Treatment Algorithm

Newly diagnosed AL amyloidosis

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

Transplant ineligible:
- Not wanting transplant: Mel-Dex or CyBorD
- ≥ 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>
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<tr>
<td>Mel/Len/Dex</td>
<td>26</td>
<td>58</td>
<td>80.8% at 2 years</td>
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<tr>
<td>Moreau et al.</td>
<td></td>
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<tr>
<td>Pom/Dex</td>
<td>33</td>
<td>48 (3)</td>
<td>76% at 1 year</td>
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<tr>
<td>Dispenzieri et al.</td>
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## Recent Studies

<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 (Cohen et al. ASH 2016)</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></td>
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<td>6/8 PI-refractory patients</td>
<td>Median OS: Not reached</td>
<td>Fatigue: most common AE</td>
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<td></td>
<td></td>
<td>Dex added in 5 pts→3 response upgrades</td>
<td></td>
<td>10 Grade 3/4 cardiopulmonary toxicities</td>
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<td><strong>Organ Responses</strong></td>
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<td></td>
<td>5 (21%) (3 kidney, 1 GI, 1 liver)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daratumumab Case Report (Sher et al. Blood 2016)</td>
<td>N= 2 MM/AL Heavily pre-treated</td>
<td><strong>Heme Response:</strong> Pt 1: CR after 8 weekly treatments</td>
<td>100%</td>
<td>Heavily Pre-treated: SCT;Bor;Imid; Dex;Carfilzomib</td>
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<td></td>
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<td>Pt 2: CR x 12 weeks</td>
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<td></td>
<td></td>
<td><strong>Organ Response:</strong> Too early</td>
<td></td>
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</tbody>
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Anti-Amyloid Therapies in AL

- Protein stabilizers
  - Doxycycline
    - Reduces fibril formation in vitro
      - (Ward et al. NEJM 2011)
    - Improved outcomes clinically
      - Mayo Clinic, London Amyloid group

- Monoclonal antibodies
  - Anti-SAP
  - 11-aF4
  - **NEOD001**: Furthest along in development
Management of AL Patients: Supportive Care

The Caregiver
Supportive Measures

- Cardiovascular drugs
- Considerable caution in use of certain medications
- Hypotension in the setting of autonomic neuropathy
- Amyloid fibrils bind to digitalis and nifedipine
- Heart transplant
Supportive Measures

- Management of pleural effusions
- Aggressive diuresis may cause hypotension and intravascular depletion
- PleurX placement
- Albumin administration
- Compression hose
Supportive Measures

- Renal involvement is common in AL
- Defined by > 500mg /day of proteinuria or serum creatinine of > 1.5 mg/dL
- ACEIs have renoprotective effects (but need to be used cautiously)
Symptomatic Treatment

- Neuropathic pain
  - Duloxetine, gabapentin, pregabalin
- Orthostatic hypotension
  - Midrodrine, fludrocortisone
- Nausea and vomiting
  - Metoclopramide, soft diet, small frequent meals
- Weakness, deconditioning
  - Physical and occupational therapy
Symptomatic Treatment

• Malnutrition and cachexia
  – Due to early satiety, abdominal bloating, n/v

• Depression
  – May become socially isolated
  – Consider amyloid support group participation

• Sexual dysfunction in males and females
  – Due to autonomic neuropathy, side effects of meds, and/or depression
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

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  – David Seldin Memorial Research Award
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Thank you!

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