Light Chain (AL) Amyloidosis
Diagnosis & Management

Michael Rosenzweig, MD
How The Experts Treat
Hematologic Malignancies
Disclosures

- Speakers Bureau:
  - Celgene
  - Akcea
Amyloidosis: Lecture Outline

- Definition & Diagnosis
  - when to suspect and how to confirm
- Classification: subtype impacts treatment
- Amyloid related organ disease
  - Involvement & Response Criteria
- Treatment & Management
  - Anti-plasma cell
  - Anti-amyloid
- hTTR Amyloidosis
Amyloidosis: 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-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>Mutant TTR</td>
<td>Peripheral/autonomic neuropathy, CMY, vitreous opacities</td>
</tr>
<tr>
<td>Mutated TTR (familial) 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</td>
<td></td>
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<tr>
<td>Afib</td>
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<tr>
<td>Alys</td>
<td></td>
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<tr>
<td>ApoA1</td>
<td></td>
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<tr>
<td>Agel</td>
<td></td>
<td></td>
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<tr>
<td>Fibrinogen alpha</td>
<td></td>
<td></td>
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<tr>
<td>Lysozyme</td>
<td></td>
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<tr>
<td>A-1 Apolipoprotein</td>
<td></td>
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<tr>
<td>Gelsolin</td>
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<tr>
<td>Renal</td>
<td></td>
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<tr>
<td>Renal (most common)</td>
<td></td>
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<tr>
<td>Renal (most common)</td>
<td></td>
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<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

• 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

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
  - Plasma cell burden often < 10%
- 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
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.
Plasma Cell Dyscrasias

MGUS

<3 g M spike
<10% PC

AND

Smoldering MM

≥3 g M spike

or

≥10% PC

No anemia, bone lesions
normal calcium and
kidney function

Active MM

≥10% PC

≥3 g M spike

AND

Anemia, bone lesions,
high calcium or
abnormal kidney function

Light Chain Amyloidosis + characteristic end organ damage

AL Amyloidosis

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
- Malabsorption

**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;

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 AND eGFR > 50 mL/min
II: Either proteinuria > 5g/24 OR eGFR < 50 mL/min
III: Both proteinuria > 5g/24 h 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

#### 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>
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</table>

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

- **1978**: SCT Phase II (N=25)
- **1996**: MPC vs C Phase III
- **1998**: SCT + MP Phase II
- **2002**: BNP Troponin
- **2004**: MDex vs SCT Phase III (N=100)
- **2007**: SCT + TD Phase II N=45
- **2011**: Bortez Phase I (N=70)
- **2014**: Ixazomib Phase III
- **2016**: Carfilzomib Phase I/II
- **2017**: Daratumumab
  - NT Pro-BNP Validated as a biomarker

1971: MPE vs MPC vs C Phase III (N=220)

1991: Case Studies MP

1997: Fibrils = FLC

2002: 2005 Criteria

2004: Thalidomide Phase 1

2005: CPHPC + Anti SAP (mice)

2009: LMD/MS

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

2015: Anti-SAP Phase I

2017: CyBorD ± Dara

CS1 expression

Validated as a biomarker

- **FLC Assay**
- **Mdex Phase II (N=45)**

City of Hope
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 CyBoR-D
  - ≥ 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
• 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

Overall Survival with HDM/SCT 1994-2014
- Median OS: 7.63 years
- Long term survival > 20 years: 29%
Hematologic Response: Critical

Overall Survival
Hematologic CR vs Non-CR

**Median OS**

- Hem-CR: not reached
- Hem non-CR: 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
<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</td>
<td>84% (2 yr OS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>39% CR (1 yr)</td>
<td>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</td>
<td>82% (2 yr OS)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>58% CR (1 yr)</td>
<td>TRM 10%</td>
</tr>
<tr>
<td>Bor/Mel Conditioning (Sanhorawala 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)</td>
<td>BD + ASCT: 95% (2 yr)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CR: 70% (2 yr)</td>
<td>ASCT: 69.4% (2 yr)</td>
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<tr>
<td></td>
<td></td>
<td>ASCT: 53.5% (1 yr)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>CR: 35% (2 yr)</td>
<td></td>
</tr>
<tr>
<td>Bor induction &amp; Bor/Mel conditioning (Sanhorawala et al. 2015.)</td>
<td>35 (30 went on to SCT)</td>
<td>100% (assessable pts) 77% (ITT)</td>
<td>TRM: 8.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>63% CR 37%VGPR</td>
<td>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

100 Patients underwent randomization

50 Were assigned to melphalan plus dexamethasone
50 Were assigned to high-dose melphalan plus stem-cell rescue

5 Died
1 Could not tolerate treatment
1 Received high-dose melphalan

43 Received 3 or more cycles of melphalan plus dexamethasone
37 Received high-dose melphalan

10 Died
1 Declined treatment
2 Did not have sufficient stem cells

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

Figure 1. Randomization, Treatment Assignments, and Receipt of Treatment.

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:

- 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
        - Mel 200 HSCT
      - No
        - Transplant ineligible
          - Mel-Dex or CyBorD
          - ≥ Hematologic VGPR
          - Clinical Trial
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
## Proteosome Inhibition: 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>
# Next Generation Proteosome Inhibitors

<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         | 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 |
| (Cohen et al. ASH 2016)        |          |                                                                                            |                        |                                                                                                |
| Ixazomib Phase I/II            | N=27     | Heme Responses  
ORR = 52%  
PFS: 14.8 months  
Organ Responses  
56% (5 renal, 5 cardiac) | 1-year PFS: 60%  
1-year OS: 85% | MTD: 4mg days  
1, 8, 15 of 28  
Grade 3 AE: Dyspnea, fatigue,  
Subcutaneous tissue disorder |
| (Sanchorawala et al. Blood, 2017) |          |                                                                                            |                        |                                                                                                |
# 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 Palladini et al.</td>
<td>31</td>
<td>48(19)</td>
<td>Not specified (60% grade 3 toxicity)</td>
</tr>
<tr>
<td>Len/Dex Sanchorawala et al.</td>
<td>34</td>
<td>67(29)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Len/Dex Dispenzneri et al.</td>
<td>23</td>
<td>41</td>
<td>Not specified</td>
</tr>
<tr>
<td>Cyclo/Len/Dex Kumar et al</td>
<td>35</td>
<td>60 (11)</td>
<td>37.8 months</td>
</tr>
<tr>
<td>Mel/Len/Dex Moreau et al.</td>
<td>26</td>
<td>58</td>
<td>80.8% at 2 years</td>
</tr>
<tr>
<td>Pom/Dex Dispenzneri et al.</td>
<td>33</td>
<td>48 (3)</td>
<td>76% at 1 year</td>
</tr>
</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.

Sanchorawala et al. ASH 2017
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

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
Treatment Algorithm

Newly diagnosed AL amyloidosis

Transplant eligible$^a$

BM PC $\geq 10\%$ or CRAB

Induction 2-4 cycles$^b$

Yes

Mel 200 HSCT$^d$

No

Not wanting transplant

Transplant ineligible$^a$

Mel-Dex or CyBoR$^d$g

$\geq$ Hematologic VGPR$^f$

Yes

Observation

Low$^e$ risk?

Yes

$\geq$ PR

No

More chemotherapy

Clinical Trial

Msmart guidelines
Mayo Clin Proc 2015
Management for Relapsed Disease

Relapsed/Refractory AL Amyloidosis

- Daratumumab Based Treatment
- CyBorD
  - VD
  - Carfilzomib
  - Ixazomib
- Mel/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
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
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”**

- Fibrillogenesis
- Surface adsorption

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

Percent change in baseline NT-proBNP (%)

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:**

  - **STABLE**
    - No renal response or progression ≥ 25% decrease in GFR
  - **RESPONSE**
    - ≥ 30% decrease in proteinuria from baseline in the absence of renal progression

  - 10 patients evaluable for response
  - 5 responders – 50%
  - 5 stable

  **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
hTTR Amyloidosis

- Due to autosomal dominant mutations encoding transthyretin (TTR)
- Mutations result in tetramer destabilization causing monomer aggregation into amyloid fibrils
- Accumulation of fibrils leads to organ dysfunction
Genetic Mutations Causing hATTR

- More than 120 TTR mutations identified
- Most common mutation worldwide is Val30Met
- V122I Most common in United States
  - 3.2 % frequency in US African Americans
New Treatments for hATTR

A: Normal transthyretin synthesis

- Wild-type TTR
- Mutant TTR
- Transcription
- Wild-type TTR mRNA
- Mutant TTR mRNA
- mRNA available for translation

Inotersen

- Wild-type TTR mRNA
- Mutant TTR mRNA
- Ribonuclease H
- Inotersen
- Target mRNA cleavage
- mRNA degradation
- mRNA available for translation greatly reduced

Patisiran

- Wild-type TTR mRNA
- Mutant TTR mRNA
- RNA-induced silencing complex
- Patisiran
- Target mRNA cleavage
- mRNA degradation
A  mNIS+7

Least-Squares Mean Change from Baseline in mNIS+7

Weeks

Placebo
Inotersen

19.7
P<0.001

8.7
P<0.001

B  Norfolk QOL-DN Score

Least-Squares Mean Change from Baseline in Norfolk QOL-DN Score

Weeks

Placebo
Inotersen

11.7
P<0.001

6.1
P=0.03
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.
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