Cardiac Amyloidosis

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Amyloidosis: What is it?

- **Amylum** – Starch (Latin)

- Generic term for *many* diseases:
  - Protein misfolds into β-sheets →
  - Forms into 8-10 nm fibrils →
  - Extracellular deposition into amyloid deposits
Types of Amyloid – Incomplete List

- **Systemic:**
  - Light chains (AL) – “Primary”
  - Transthyretin (ATTR) – “Senile” or “Familial” or “FAC” or “FAP”
  - Serum amyloid A (AA) – “Secondary”

- **Localized – Not to be memorized!**
  - Beta-2 microglobulin (A-β2) – Dialysis (osteoarticular structures)
  - Apolipoprotein A-1 (AApoA-I) – Age-related (aortic intima, cardiac, neuropathic)
  - Apolipoprotein A-2 (AApoA-2) – Hereditary (kidney)
  - Calcitonin (ACal) – Complication of thyroid medullary CA
  - Islet amyloid polypeptide (AIAPP) – Age-related (seen in DM)
  - Atrial natriuretic peptide (AANF) – Age-related (atrial amyloidosis)
  - Prolactin (APro) – Age-related, pituitary tumors
  - Insulin (AIns) – Insulin-pump use (local effects)
  - Amyloid precursor protein (ABeta) – Age-related/hereditary (Alzheimers)
  - Prion protein (APrPsc) – Hereditary/sporadic (spongiform encephalopathies)
  - Cystatin-C (ACys) – Hereditary (cerebral hemorrhage)
  - Fibrinogen alpha chain (AFib) – Hereditary (kidney)
  - Lysozome (ALys) – Hereditary (Diffuse, especially kidney, spares heart)
  - Medin/Lactadherin – Age-related (medial aortic amyloidosis)
  - Gelsolin (AGel) – Hereditary (neuropathic, corneal)
  - Keratin – Cutaneous
AL: A Brief Dive into Hematology…

- Plasma cells: Make antibodies
- Antibodies: Made up of light chains & heavy chains
  - Light chain: Two types (κ and λ) – determine part of antibody’s specificity
- What happens when someone develops a clonal plasma cell population?
Plasma Cells Gone Wrong

Three things happen:
- Plasma cell clones take over % of bone marrow
- Plasma cells produce a clonal antibody (IgG-\(\lambda\))
- Plasma cells produce excess light chain (\(\lambda\))

Possible outcome 1:
- Only small % of marrow taken over, circulating light chains don’t deposit \(\rightarrow\) MGUS

Possible outcome 2:
- Large % of marrow taken over (and possible consequences thereof) \(\rightarrow\) Myeloma

Possible outcome 3:
- Circulating light chains deposit in tissue \(\rightarrow\) AL Amyloidosis

Note: Possibilities 2 & 3 can coexist – but don’t have to
Transthyretin (TTR)

- Transthyretin = “**Transports thyroxine and retinol**”
  - Prealbumin by any other name…

- Almost completely circulates as a tetramer
  - In steady-state with monomeric form

- Monomeric TTR is inherently ‘amyloidogenic’

- Mutations in TTR can make it even more amyloidogenic
Wild-Type “Senile” ATTR Amyloidosis

- Normal transthyretin protein
- Almost exclusively deposits in heart
  - Men >>> Women
  - Previously called “benign deposits” in hearts of elderly
Study of wtTTR Amyloid Prevalence

- Study from Mayo Clinic published in April 2014
- Reviewed autopsies from:
  - 109 patients with antemortem diagnosis of HFpEF without any clinical suspicion of amyloidosis
  - Age-matched control patients without antemortem HF diagnosis
- Blinded pathology review

Familial ATTR Amyloidosis

• Predominant manifestations:
  • Cardiomyopathy
  • Peripheral neuropathy

• Dozens of mutations described!
  • Type of mutation correlates with severity, age of onset, and clinical manifestations of disease
  • V30M mutation: Most common in Portugal (1/600)
    • Familial amyloid polyneuropathy (“FAP”)
  • V122I mutation: Seen in 3-4% of individuals of African descent (!)
    • By far the most common mutation encountered in USA
    • Familial amyloid cardiomyopathy (“FAC”)


Spectrum of Disease By Mutation

- Neuropathy
- Cardiomyopathy
- V30M
- T60A
- V122I
- Wild-type
V-122I: How Common, How Important?

• 3856 black participants in Atherosclerosis Risk in Community (ARIC) study recruited from 1987-1989
  • Note: Only 36% male, average age 52 at entry
• Each participant genotyped for TTR gene
• Findings:
  • Mutation in self-reported black population: 124/3732 (3.2%)
  • Mutation in non-black population: 2/10893 (0.02%)
  • More systolic/diastolic dysfunction, higher NT-BNP in V-122I carriers
    • 7% of carriers with overt amyloid CM

Adapted from Quarta et al. NEJM. 2015. 372:21-9.
Clinical Presentation and Diagnosis
Amyloidosis: Diagnosis

“The only way to diagnose amyloidosis is to consider the diagnosis.”
AL Amyloidosis: Clinical Features

■ Multiorgan system involvement:
  – Cardiac: Heart failure, arrhythmias, hypotension, imaging abnormalities
  – Renal: Proteinuria, renal failure
  – Neurologic: Peripheral neuropathy, autonomic dysfunction
  – GI: Dysphagia, malabsorption, GI bleeding, constipation, nausea, liver dysfunction (alk phos elevation)
  – Soft tissue/ENT: Macroglossia, carpal tunnel syndrome, voice changes, nail changes
Cardiac Manifestations

- Heart failure
  - Diastolic dysfunction > Systolic dysfunction
- Electrophysiologic
  - Heart block
  - Tachyarrhythmias
  - Low voltages on EKG (*)
- Imaging/Laboratory
  - Left ventricular “hypertrophy”
  - Elevated troponin
Cardiac Amyloid: Diagnosis by Imaging

- Increased ventricular thickness
  - RV thickened as well

- Combination of increased ventricular mass & low voltages → quite specific for amyloid.
Typical EKG in Cardiac Amyloidosis
Which of These is Amylodiosis?
Which of These is Amylodiosis?

Answer: Both!
How to Diagnose – Biopsy!

- Cannot r/o with lab assessment
- Technetium-pyrophosphate scans?
- Our general practice:
  - Biopsy of clinically involved organ
- Testing for amyloid subtype – plan ahead!
  - Know thy pathologist
  - Congo Red
  - Immunofluorescence or Mass spectrometry

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<th>Organ</th>
<th>Sensitivity</th>
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<td>Abdominal fat pad</td>
<td>“70%” (?)</td>
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<td>Bone marrow</td>
<td>50-56%</td>
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<tr>
<td>Rectal</td>
<td>70-85%</td>
</tr>
<tr>
<td>Clinically involved organ</td>
<td>Nearly 100%</td>
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</table>
Adjunctive Laboratory Tests

- SPIEP: Looks for monoclonal immunoglobulins in serum
- UPIEP: Looks for monoclonal light chains in urine (enriched in urine)
- Free light chain assay: Measures ratio of $\kappa$ to $\lambda$ in serum
  - Normal ratio: Approximately 1:1
  - If significant excess: Implies monoclonal light chain production
  - Main assay to assess hematologic response to Rx
- BNP, Troponin, alkaline phosphatase, urine albumin:Cr ratio
- TTR amyloidosis: Genetic testing
AL Amyloid Treatment Strategy: Parallel Paths

- Treatment of consequences of organ dysfunction

- Treatment of clonal plasma cell disorder
  - Chemotherapy
  - Stem cell transplant
Treatment: Cardiac-Specific

- Diuretics/salt restriction
  - Often have large amounts of peripheral edema/ascites
- To generally be avoided:
  - Digoxin
  - Beta-blockers
  - Calcium-blockers
  - Vasodilators (ACE-I/ARBs)
- Midodrine
  - Can be useful in orthostatic hypotension
- Treatment of atrial & ventricular arrhythmias
Sudden Death in Amyloidosis – The Old Paradigm

• “Most sudden death is due to EMD/hypotension, not arrhythmias. Don’t place an ICD!”

• “ICDs don’t work in amyloidosis. They usually fail to convert the rhythm!”

• “ICDs don’t work in amyloidosis. Even when they do convert the rhythm, the patient is left in PEA!”

• “The prognosis is terrible in amyloidosis – why would you want to convert a peaceful sudden death to a miserable heart-failure-with-gruesome-shocks death?”
ICDs: Mayo Data (2000-2009)

- 53 patients with cardiac amyloidosis underwent ICD placement (41 primary prevention, 12 secondary prevention)
- Appropriate ICD shocks in first year = 32% (!)
- AL more likely to receive appropriate shocks than ATTR
- No clear survival advantage, though...
  - Underpowered to detect difference
  - Many of the patients met ‘traditional’ ICD indications (probably too late given low LVEF = late finding)
  - Study conducted before development of many of the newer chemotherapy regimens

ICDs: Stanford Data (2008-2012)

- 31 consecutive patients with cardiac involvement but without advanced heart failure → ambulatory telemetry monitoring
- 23/31 (74%) patients with NSVT
  - ICDs placed in 19 patients
- 6 patients with ICDs had sustained VT
  - Rhythm successfully broken in 5/6 patients
- Our practice – ICD consideration if life expectancy >1 year and:
  - History of non-postural syncope or
  - VT seen on ambulatory telemetry

AL Amyloidosis –
Prognosis & Chemotherapy Approaches
Immunoglobulin light chain amyloidosis (AL)

- **Heart** 76%
  - (NYHA≥II, 47%)
- **Kidney** 68%
  - Nephrotic s. 42%
  - Renal failure 45%
- **Liver** 15%
- **GI** 8%
- **Soft tissues** 17%
- **PNS/ANS** 12%/10%

Organ dysfunction and reduced survival

Interactions with cells & microenvironment (GAGs, metals, proteases, shear forces) of target organs

Adapted from Merlini
Plasma cells and immunoglobulin light chains?

• Plasma cells produce immunoglobulins
  – Heavy chain IgG, A, M, D, E,
  – Light chain: kappa and light chain

• Serum free light chain levels can now be measured (FreeLite, The Binding Site)
  – Plasma cell production
  – Renal clearance

• Some light chains have amyloidogenic potential
Spectrum of plasma cell disorders

- **MGUS**
  - Low risk
  - Int/high risk

- **SMM**
  - Low risk
  - High risk

- **Multiple myeloma**
  - Biomarker of malignancy
  - Myeloma defining event

**Tumor progression**

- Genetic, epigenetic and microenvironmental abnormalities

**M-protein disease**

- Monoclonal gammopathy
  - IgG/IgA/light chain

- End-organ damage

**MGRS and others**

- AL amyloidosis

**Survival**
AL amyloidosis is not multiple myeloma

**Amyloidosis**
- Low tumor burden
- Protein-mediated organ dysfunction

**Multiple myeloma**
- High tumor burden
- Tumor-mediated organ dysfunction

**Amyloidosis & multiple myeloma**
- High tumor burden
- Protein- and tumor-mediated organ dysfunction
Outcomes in AL amyloidosis

- Overall survival is improving due to novel agents for multiple myeloma
- Early mortality appears to be improving

**Mayo Clinic 2000-14**

**Sweden 1995-2013**

Prognosis in AL – Mayo 2004 staging

- Extent of cardiac involvement in AL drives outcome
- Mayo Clinic study of 261 AL patients seen between 1979-2000
- Factors
  - cTnT <0.035 ug/L
  - NT-pro-BNP <332 ng/L

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<th>Median OS (mos)</th>
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<td>30</td>
<td>10.5</td>
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<tr>
<td>III</td>
<td>37</td>
<td>3.5</td>
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Prognosis in AL – Mayo 2012 staging

- Cardiac involvement + plasma cell clone
- Factors
  - cTnT ≥ 0.025 ng/mL
  - NT-proBNP ≥ 1,800 pg/mL
  - FLC-diff ≥ 180 mg/L

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<tr>
<td>IV</td>
<td>23</td>
<td>5.8</td>
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Kumar S J Clin Oncol 2012
Goals of therapy in AL amyloidosis

• Obtain rapid, deep and sustained clonal remissions
  – Defined by serum free light chain response
  – Hematologic “very good partial remission” = FLC-diff <40 mg/L or better
• Reducing toxic serum free light chains
  – Improves cardiac function
  – Allows for clearance of tissue amyloid by native immune system
• Interfere with amyloid formation?
• Stimulate therapeutic clearance of amyloid from tissues?
• Prolong survival
• Cure?
Therapeutic approaches to AL amyloidosis

Modified from Weiss Blood 2016
Achieving a deep hematologic remission is the key to prolonged survival – but how to get there?

HDM/ASCT
Boston University 1994-2014
n = 629

Chemotherapy (CyBorD)
UK NAC & Pavia 2006-2013
n = 230

4 years

Sanchorawala Blood 2015, Palladini Blood 2015
## HDM/ASCT Pro-Con

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<tr>
<th>Pro</th>
<th>Con</th>
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<tr>
<td>Favor HDM/ASCT</td>
<td>Favor chemotherapy</td>
</tr>
<tr>
<td>• Deep hematologic responses</td>
<td>• RCT favors chemotherapy</td>
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<tr>
<td>• Durable responses—most &gt;10 year survivors have had ASCT</td>
<td>• All patients are candidates</td>
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<tr>
<td>• Matched-case control favors HDM/ASCT</td>
<td>• Hematologic responses comparable</td>
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<tr>
<td>• Transplant related mortality now 3-5%</td>
<td>• Toxicity low</td>
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<tr>
<td></td>
<td>• Treatment related morality &lt;2%</td>
</tr>
<tr>
<td></td>
<td>• Many agents available to achieve response</td>
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An individualized, risk-adapted, multi-disciplinary treatment plan by clinicians experienced in amyloidosis is required for all patients.

Sher Biol Blood Marrow Transplant 2016, Devine Biol Blood Marrow Transplant 2014
Who is eligible for HDM/ASCT?

• Only about 25% of all patients are eligible

• Criteria (Mayo)
  – ”Physiologic” age ≤70 years
  – Troponin T <0.06 ng/mL,
  – CrCl ≥30 mL/min (unless on HD)
  – NYHA I/II
  – No more than 2 organs significantly involved (liver, heart, kidney, autonomic nerve)

The role of HDM/ASCT is diminishing, in particular for cardiac amyloidosis
Doxycycline may reduce early death in cardiac AL

- Doxycyline may be cardioprotective
  - Interfere with amyloid fibril formation
  - May accelerate amyloid clearance
  - Reduces cardiotoxicity of light chains

- Matched case-control study from UK NAC

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<td>Patients, n</td>
<td>30</td>
<td>73</td>
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<tr>
<td>Hematologic CR/VGPR, %</td>
<td>56/10</td>
<td>35/8</td>
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<tr>
<td>Cardiac response, %</td>
<td>60</td>
<td>18</td>
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<tr>
<td>Median OS, months</td>
<td>NR</td>
<td>13</td>
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<td>12 month survival, %</td>
<td>82</td>
<td>53</td>
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<tr>
<td>24 month survival, %</td>
<td>82</td>
<td>40</td>
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Wechelakar ASH 2015
An approach to AL amyloidosis for 2017

High plasma cell burden
FLC-diff ≥180
BMPCs ≥10%
AL + CRAB

Yes

Transplant eligible

No

Cardiac involvement
Not a candidate for anti-amyloid MoAb trial

Declines

CyBorD or Mel-Dex-Bor³

≥ Hematologic VGPR

Yes

Observation

No

Doxycycline 100 mg bid for 6-12 months

CyBorD
Mel-Dex
Mel-Dex-Bor

Induction therapy
2-4 cycles¹

Mel 200 ASCT²

¹Or if delay in moving to ASCT
²Mel 140 if on chronic HD.
³Do not use Mel if candidate for ASCT in second line.
⁴Daratumumab preferred if insurance approval.
Therapeutic approaches to AL amyloidosis

Clonal plasma cell disorder

Amyloidogenic Ig Light chains → Multi-step process of oligomer formation → Amyloid Fibrils

Doxycycline
EGCG
mAb 11-1F4
mAb anti-SAP
mAb NEOD001

Organ dysfunction and deposition

High-dose melphalan/AutoSCT
Melphalan-dexamethasone
Bortezomib-based regimen (CyBorD)
IMiD-based regimens
Daratumumab
Eloctuzumab
Venetoclax

Standard care
Investigational

Reduction or interference
Possible reduction or interference
Direct organ toxicity
Enhances phagocytic clearance

Modified from Weiss Blood 2016
NEOD001 in AL amyloidosis

- NEOD001 is a monoclonal antibody that targets epitope on amyloid deposits.
- Believed to trigger phagocytic clearance by macrophages.
- Phase 1 study of monthly IV infusions in patients with persistent organ dysfunction after chemotherapy.
- Safe with encouraging cardiac and renal responses.

Cardiac-Evaluable Patients (N = 14)
- Eight responders (57%)
- Six stable (43%)

Renal-Evaluable Patients (N = 15)
- 9 responders (60%)
- 6 stable (40%)
What about the impact of prior chemotherapy?

- **NEOD001** induces organ improvement in patients in long-term hematologic remissions
  - Patient 1: Renal response 40 months after hem CR
  - Patient 2: Cardiac response 10 months after hem CR

Treatment: ATTR Amyloidosis
ATTR Amyloidosis: Traditional View

- Wild-type ("senile") ATTR:
  - Supportive Rx only

- Familial ATTR: Early liver transplant
  - TTR is almost exclusively produced by the liver
  - If replaced the liver → remove mutated TTR protein → slow or halt disease progression
  - Used primarily for "FAP"
    - Early age of onset
    - Disabling neuropathy
Strategies to Prevent TTR Amyloid Deposition

- Stabilize tetrameric form of TTR by binding to L-thyroxine receptor
  - Tafamidis
  - NSAIDs (diflunisal)
  - Other investigational agents...
    - Tolcapone
    - AG10

- Inhibit production of TTR in all forms
  - RNA inhibition/interference
Tafamidis Trial in “FAP”

- Phase 3 trial conducted at 8 sites in Europe & South America

- 128 patients with FAP due to V30M mutation randomized to tafamidis or placebo x 18 months
  - Primary endpoint: “Responder” or “Nonresponder”
  - Occurrence of liver transplant → “Nonresponder”
    - 69% on liver transplant list at start of study (!)
    - 13 patients in each group (21%) transplanted during study
Tafamidis FAP Trial

Secondary Endpoints

Tafamidis Approval for FAP
Tafamidis Approval for FAP
Tafamidis Approval for FAP
ATTR-ACT Study – Tafamidis for ATTR Cardiomyopathy

- Phase 3, Randomized, Placebo-Controlled clinical trial of tafamidis for ATTR cardiomyopathy
  - Wild-type or familial
  - 441 patients worldwide x 2.5 years
  - Primary endpoint: Mortality & CV Hospitalization
  - Completed enrollment summer, 2015
NSAIDs/Diflunisal

- NSAIDs – Found on screening to stabilize transthyretin
- Diflunisal: FDA approved for arthritis pain
  - Found to be most effective NSAID at binding to TTR
- Double-blind, placebo-controlled clinical trial for FAP reported in December, 2013

Adapted from Berk et al. JAMA. 2013;310:2658-2667.
Diflunisal Study: NIS+7 Score

Adapted from Berk et al. JAMA. 2013;310:2658-2667.

Change from baseline

P=.02
P<.001

Placebo
Diflunisal

Adapted from Berk et al. JAMA. 2013;310:2658-2667.
RNA Interference & Antisense

- RNA interference (ALN-TTR)
  - Decreases circulating TTR by approximately 85%
  - IV form:
    - Phase 3 study (IV) in FAP – “APOLLO”
      - 225 patients x 18 months
      - Estimated completion: August, 2017
  - Sub-Q form:
    - Phase 3 study in FAC – “ENDEAVOUR”:
      - Stopped early due to excess mortality in treatment arm

- Antisense Technology (IONIS-TTR)
  - Phase 2/3 Study (SQ) in FAP currently ongoing
    - 195 patients x 64 weeks
    - 2016: Concerns raised re: thrombocytopenia
  - Cardiac trial originally planned... Now not.
Summary of Clinical Trials

- Polyneuropathy (“FAP”)
  - Tafamidis (oral):
    - Borderline positive results → Approved in Europe/Japan, not USA
  - Diflunisal (oral): Positive trial
  - ALN-TTR (IV): Current phase 3 trial
  - IONIS-TTR (SQ): Current phase 2/3 trial

- Cardiomyopathy
  - Tafamidis (oral): Current phase 3 trial (ATTR-ACT) – Wild-type & FAC
    - Enrollment completed
  - ALN-TTR (SQ): Phase 3 trial (ENDEAVOUR) – Stopped early due to harm
  - IONIS-TTR: Planned trial halted before it began
Heart Transplant: Is it Crazy?

- 1980s-1990s: Amyloid outcomes when transplanted → Terrible
  - Mainly AL amyloidosis, mainly late, poor chemotherapy options!
- Patients died from:
  - Multiorgan dysfunction from amyloid infiltration
  - Recurrent amyloid deposition in new graft
- But what if…
  - Patients were selected who had little-no significant extracardiac involvement
  - Patients received effective chemotherapy as part of their treatment
Early 2000s: Still Discouraging…

  - 24 transplants for amyloid (17 AL)
  - Median survival: 29 months
  - AL amyloid: 59% 1-year survival

- 2005: Report on all 69 patients transplanted in USA per UNOS 1987-2002
  - 1-year survival: 74.6%
  - 5-year survival: 54.0%
  - Worse than nonamyloid transplant survival (P=0.03)
  - Men survived longer than women
    - ? Surrogate for ATTR vs. AL

Mayo Experience

• Reported on 11 patients who underwent heart transplant for AL amyloidosis from 1994-2005
• All were screened for evidence of significant extracardiac organ involvement
• All underwent sequential heart transplant → SCT
• Outcomes:
  • Worse than average heart transplant...
  • But acceptable?

Stanford Experience

- Stanford 2008-2013: 19 transplants for end-stage cardiac amyloidosis – data published in 2015
  - AL: 9 patients
  - ATTR: 10 patients
- Current status: 22/24 (92%) transplanted since 2008 are alive
  - AL: 10/10 patients alive
    - 9 with no deposition up to >8 years out
    - 1 with mild deposition in new graft
    - Not all automatically slated for SCT
  - ATTR: 12/14 patients alive
    - 2 deaths (unrelated to amyloid)
    - 12 patients without recurrent amyloid deposition in new graft

High Wait-List Mortality: MGH Experience 2000-2011 of 31 patients listed for OHT

Adapted from Gilstrap et al. J Heart Lung Transplant. 2014;33:149-156
Heart Transplant: National Data

- UNOS Registry: Amyloid vs. Other RCM vs. All others
- Could not differentiate AL from ATTR

Findings:
- Era 1: 111 amyloid/36483 total (0.3%)
- Era 2: 110 amyloid/9383 total (1.2%)
- Demographics: Era 2 = Older, higher % black, higher % male (compared with Era 1)
- Survival significantly better in Era 2 vs. Era 1 for amyloid patients (unchanged for other RCM patients)
- Survival not statistically different from overall cohort or other RCM patients in Era 2 (much worse in Era 1)

Adapted from Davis et al. J Heart Lung Transplant. 2015;34:658-66.
Figure 2  (A) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs all other diagnoses in Era 1 (1987 to 2007). (B) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs all other diagnoses in Era 2 (2008 to 2013). (C) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs other restrictive cardiomyopathies (RCM) undergoing heart or heart-liver transplantation in Era 1 (1987 to 2007). (D) Unadjusted post-transplant survival of patients with amyloid cardiomyopathy (ACM) vs other restrictive cardiomyopathies (RCM) undergoing heart or heart-liver transplantation in Era 2 (2008 to 2013).
Case #1

- 70 year-old Caucasian man
- Elevated screening PSA → Prostate CA → Radical prostatectomy
- Following 2 months:
  - LE/scrotal edema
  - TTE → moderate concentric LVH, normal systolic function, severe diastolic dysfunction, RVSP = 52 mmHg.
  - EKG performed
Case Presentation #1

• Laboratory studies:
  • SPIEP: Trace IgM-lambda monoclonal spike
  • Serum free light chain assay:
    • Significantly elevated free lambda light chain

• Bone marrow biopsy
  • Small lambda-restricted plasma cell population
  • + Amyloid deposits in blood vessels

• Referred for consideration of the best chemotherapy options
Which is the Best Option?

1) Autologous stem cell transplant (ASCT)

2) Proteasome inhibitor-based regimen (e.g. CyBorD)

3) Daratumumab

4) None of the above – the diagnosis still isn’t clear
What Happened...

- Pathology sent for mass spectrometry:
  - Amyloid deposits = TTR (!), wild-type
- Endomyocardial biopsy
  - Diffuse amyloid involvement → stained strongly for TTR
- Clinical course
  - ATTR amyloidosis
    - Symptomatic treatment
    - Enrolled in tafamidis Phase 3 trial
  - MGUS – no chemotherapy indicated
  - Doing well >3 years since diagnosis
Question #2

- **Case presentation**
  - 63 year-old female with
    - Severe fatigue and nausea
    - Multiple episodes of presyncope
    - Pain and tingling in legs and hands
    - Dyspnea on exertion and lower extremity edema
    - 20 pound weight gain
- Exam: BP 70/44 P 117, 4+ edema
- Laboratory data
  - NT-proBNP 10,744, troponin T 0.3
  - 24 hour urine protein 12 grams

A Congo Red stain is positive on an aspirate of abdominal fat. The serum free light chain differential is 250 mg/L and a bone marrow biopsy shows 15% lambda-restricted plasma cells.

**Question**
What anti-plasma cell therapy is clearly contraindicated in this patient?
A. Cyclophosphamide and prednisone
B. Melphalan and dexamethasone
C. Bortezomib and dexamethasone
D. High-dose melphalan and autologous stem cell transplantation
Answer Question #2

- High dose melphalan and ASCT is contraindicated in this patient due to NT-proBNP >5,000, positive troponin T and systolic blood pressure <90.
- Bortezomib is relatively contraindicated in this patient given the SBP <90. A trial of midodrine and/or fludricortisone can increase the blood pressure to allow for use of bortezomib.
- The other regimens can be given with careful attention to the patient’s volume status and would be preferred if attempts to raise the blood pressure were unsuccessful.
Take Home Points

• Think about amyloidosis!
• Importance of determining subtype
• Amyloidosis ≠ death sentence
• AL amyloidosis treatments:
  • We have effective chemotherapy now
  • Hematologic response is key to controlling the disease
  • Emerging therapies to target amyloid deposits
• ATTR: Emerging therapies in clinical trials
  • But some recent hiccups
• Role of ICDs/heart transplant
• Importance of multidisciplinary approach, centers of excellence, clinical trials