Update on Treatments for Systemic Amyloidosis

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ANZSN Update Course
Darwin, Australia
September 2, 2017
Most of the treatments that will be discussed are not approved for amyloidosis.
The development of new treatment approaches during the past 15 – 20 years has resulted in remarkable improvements in outcomes.
What is Amyloidosis?

Group of diseases in which a protein that is normally soluble deposits extracellularly in tissues as insoluble fibrils that have a specific biochemical structure.
# Systemic Amyloidoses

<table>
<thead>
<tr>
<th>Category</th>
<th>Precursor Protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL (Primary)</td>
<td>Ig Light Chain</td>
</tr>
<tr>
<td>AA (Secondary)</td>
<td>Serum AA (SAA)</td>
</tr>
<tr>
<td>Hereditary</td>
<td>TTR, lysozyme, fibrinogen, ApoA1, ApoA2, ApoA4, gelsolin</td>
</tr>
<tr>
<td>Senile Systemic</td>
<td>TTR</td>
</tr>
<tr>
<td>ALect2</td>
<td>Lect2</td>
</tr>
<tr>
<td>Dialysis-Related</td>
<td>(\beta_2) microglobulin</td>
</tr>
</tbody>
</table>
Amyloidogenic Proteins Differ Functionally and Structurally

- IgG Kappa
- Apolipoprotein A-I
- Lysozyme
- Transthyretin
- A-beta
- Beta 2M
But Resulting Amyloid is Morphologically Indistinguishable
But Resulting Amyloid is Morphologically Indistinguishable

Lambda LC

Kappa LC
Laser Capture Microdissection / Mass Spectrometry for Typing Amyloid

Partial List of Manifestations

- Kidney: nephrotic syndrome, progressive renal failure
- Heart: restrictive cardiomyopathy
- Liver: hepatomegaly
- GI tract: bleeding, malabsorption
- Nervous system: autonomic or peripheral neuropathy
- Endocrinopathies: thyroid, adrenal
- Soft tissue disease: dermopathy, carpal tunnel syndrome, muscle involvement
Disorder of Protein Misfolding

- Mutation
- Proteolytic event
- Local environmental factors

Soluble Precursor  →  Unstable Variant
Disorder of Protein Misfolding

Mutation
Proteolytic event
Local environmental factors

Soluble Precursor → Unstable Variant → Folding Intermediate

→
Disorder of Protein Misfolding

- Mutation
- Proteolytic event
- Local environmental factors

Soluble Precursor → Unstable Variant → Folding Intermediate → Self-Aggregation

- Disorder of Protein Misfolding
Disorder of Protein Misfolding

Mutations
Proteolytic event
Local environmental factors

Soluble Precursor → Unstable Variant → Folding Intermediate → Self-Aggregation → Amyloid Fibril

Amyloid Fibril
Disorder of Protein Misfolding

Mutation
Proteolytic event
Local environmental factors

Soluble Precursor → Unstable Variant → Folding Intermediate → Self-Aggregation

Degradation ← Amyloid Fibril
How Does Amyloid Cause Disease Manifestations?

Unstable Fragment or Variant \(\rightarrow\) Folding Intermediate \(\rightarrow\) Self-Aggregation

Tissue
“The Amyloid Hypothesis”

Unstable Fragment or Variant $\leftrightarrow$ Folding Intermediate $\leftrightarrow$ Self-Aggregation

Tissue

Amyloid Fibrils
Revised “Amyloid Hypothesis”

Unstable Fragment or Variant → Folding Intermediate → Self-Aggregation → Amyloid Fibrils

Tissue
Revised “Amyloid Hypothesis”
Revised “Amyloid Hypothesis”
Multiple Potential Treatment Targets

Soluble Precursor -> Unstable Variant -> Folding Intermediate -> Self-Aggregation

Degradation <-> Amyloid Fibril
Treatment Targets

- Precursor Protein Production
- Unstable Variant Formation
- Fibril Formation
- Tissue Deposition
- Protease Resistance
Treatment Target 1

- Precursor Protein Production
- Unstable Variant Formation
- Fibril Formation
- Tissue Deposition
- Protease Resistance
# Anti-Plasma Cell Therapy for AL Amyloidosis

## Melphalan and Prednisone

   - Melphalan/Prednisone/Colchicine: 12 months
   - Colchicine: 7 months

2. Kyle et al, NEJM 1999
   - Melphalan/Prednisone: 18 months
   - Melphalan/Prednisone/Colchicine: 17 months
   - Colchicine: 8 months
High-Dose Melphalan with Autologous Stem Cell Transplantation

G-CSF

Stem Cell Infusion

I.V. Melphalan

Stem Cell Collection
Treatment Toxicities

- Heart Failure
- Anasarca, capillary leak syndrome
- Splenic Rupture
- Arrhythmias
- Sepsis, infection
- Gastrointestinal bleeding
- Mucositis
- Acute Kidney Injury
Tolerability Improves with Experience

- 1994-2000: 14%
- 2000-2005: 9%
- 2005-2014: <3.4%

Sanchorawala et al. ASH 2014, Blood 2015
Boston University Experience with HDM/SCT
1994-2014

Median Survival 7.6 years

Sancho rawala et al Blood 2015
Impact of Hematologic Response on Survival

Complete Response
Median Not Yet Reached

Non-Complete Response
Median 6.3 yrs

Sanchorawala et al Blood 2015
Proteinuria Improves with Hematologic Remission

Urine Protein

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>10 g/24 hr</td>
<td>2 g/24 hr</td>
</tr>
<tr>
<td>Persistent Disease</td>
<td>9 g/24 hr</td>
<td>1 g/24 hr</td>
</tr>
</tbody>
</table>

Creatinine Clearance

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>100 ml/min</td>
<td>75 ml/min</td>
</tr>
<tr>
<td>Persistent Disease</td>
<td>90 ml/min</td>
<td>70 ml/min</td>
</tr>
</tbody>
</table>

Summary: High-Dose Melphalan with ASCT for AL Amyloidosis

• Can produce a complete hematologic remission in a substantial proportion of patients

• Complete hematologic remission is associated with prolonged survival and with improvement in organ function

• Complete hematologic remission is more likely with higher dose of melphalan

• The hematologic response appears to be durable

• Treatment toxicity is prohibitive for many patients
Additional Anti-Plasma Cell Agents

- Bortezomib
- Carfilzomib
- Ixazomib
- Lenalidomide
- Pomalidomide
- Daratumumab

All target the source of the amyloidogenic protein
Treatment Decisions are Challenging

Alternatives to autologous stem cell transplantation are less intensive but.....

– Treatment is prolonged
– Unclear when to expect response
– Unclear how long to treat
– Durability of response not as well established
Treatment Targets

• Precursor Protein Production ✔
• Unstable Variant Formation
• Fibril Formation
• Tissue Deposition
• Protease Resistance
Treatment Targets

- Precursor Protein Production ✔
- Unstable Variant Formation - TTR
- Fibril Formation
- Tissue Deposition
- Protease Resistance
Treatment Targets

- Precursor Protein Production ✓
- Unstable Variant Formation - TTR
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Multiple Potential Treatment Targets

- Soluble Precursor
- Unstable Variant
- Folding Intermediate
- Self-Aggregation
- Degradation
- Amyloid Fibril
Serum Amyloid P (SAP)

- SAP is a plasma glycoprotein, member of the pentraxin family
- Present in all amyloid deposits
- Exists in dynamic equilibrium between plasma and tissue
SAP and Amyloid

- SAP is highly resistant to proteolysis and protects amyloid fibrils from degradation \textit{in vitro}.
- Thought to contribute to failure to clear amyloid deposits \textit{in vivo}.
SAP is in Equilibrium between Plasma and Tissue (amyloid-bound)
CPHPC Binds to Circulating SAP

Pepys et al, Nature 2002
CPHPC Binds to Circulating SAP

Pepys et al, Nature 2002
CPHPC Depletes SAP from Plasma (and Secondarily from Tissue)

Pepys et al, Nature 2002
CPHPC Depletes SAP from Plasma (and Secondarily from Tissue)

Pepys et al, Nature 2002
Without SAP, Amyloid is Degraded by Endogenous Proteases

Pepys et al, Nature 2002
Results with CPHPC

• CPHPC infusion depleted SAP from tissue amyloid deposits in murine AA amyloidosis and in hSAP transgenics.

• In humans, CPHPC infusion was accompanied by nearly complete clearance of SAP from plasma.

• What happens to amyloid deposits????

Pepys et al, Nature 2002
2010: CPHPC Coupled with Anti-SAP Ab

- Some SAP remains in amyloid deposits after CPHPC treatment
- New approach: deplete SAP from circulation using CPHPC and then administer anti-SAP Ab
  - Goal is to trigger endogenous mechanisms for clearing anti-SAP-amyloid complexes
  - Dense macrophage infiltration observed at site of amyloid deposits
  - Clearance of amyloid in mouse models

Bodin K et al. Nature 2010; 468:93-7
2010: CPHPC Coupled with Anti-SAP Ab

• Some SAP remains in amyloid deposits after CPHPC treatment

• New approach: administer anti-SAP Ab after CPHPC-induced depletion of SAP from circulation
  – Goal is to trigger endogenous mechanisms for clearing anti-SAP-amyloid complexes
  – Dense macrophage infiltration observed at site of amyloid deposits
  – Clearance of amyloid in mouse models
  – **What happens in humans??**

Bodin K et al. Nature 2010; 468:93-7
CPHPC Coupled with Anti-SAP Ab: Phase 1 Human Study

N Engl J Med 2015; 373:1106-1114

- Open-label, phase 1 study, 15 patients with AL, AA, Afib, or AApoA1 amyloidosis
- CPHPC followed by humanized monoclonal anti-SAP antibody
- Well-tolerated
- SAP cleared from circulation
- Decreased SAP in liver and kidney tissue
- Reduction in liver stiffness, liver volume
Anti-LC Amyloid Antibody: “NEOD001”

Targets epitope of misfolded LCs and triggers Ab-mediated phagocytosis

Gertz et al JCO 2015
NEOD001 Early Experience

NEOD001 Trials

• **PRONTO**
  – Cardiac involvement, prior anti-plasma cell therapy, no current therapy
  – Placebo-controlled, 100 participants
  – Primary outcome: change in NT-proBNP
  – Completion expected Jan 2018

• **VITAL**
  – Cardiac, treatment-naïve, concurrent anti-plasma cell therapy
  – Placebo-controlled, 236 participants
  – Primary outcome: cardiac mortality or cardiac hospitalization

• **RAIN**
  – Renal involvement, prior anti-plasma cell therapy, no current therapy
  – Placebo-controlled, 100 participants
  – Primary outcome: renal response
  – Not yet started
Why So Much Progress in Amyloidosis?

- Fascination by biochemists, biophysicists, structural biologists with these protein folding disorders

- Vibrant collaboration between basic scientists and clinicians

- Tremendous efforts by patient support groups and rare disease organizations as well as interest by industry
University of Pennsylvania
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Jonathan Hogan

Oncology
Brendan Weiss
Adam Cohen
Daniel Vogl
Edward Stadtmauer

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