Multiple Myeloma: Contemporary Therapies and Cardiovascular Challenges

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The patient, Sarah Newbury, was a 39-year-old housewife who had developed severe back pain. She died 4 years after the onset of symptoms, and the postmortem examination revealed that a red substance had replaced the cancellous portion of the sternum as well as both femurs. Autopsy revealed fractures of the right radius and ulna, left tibia and fibula, and both femurs.
Multiple Myeloma

- 1% of cancer
- 10% of all hematological malignancies
- 2-3x more frequent in blacks
- Males to females is 1.4:1
- Median age of diagnosis is 68 years
- Single clone of plasma cells producing a monoclonal immunoglobulin
B-Cell Maturation and Neoplasms

“Cell of origin”

Bone marrow

Myeloma cells (plasma cells)

Blood stream (and urine)

Intact immunoglobulins

heavy chains + light chains

Immunoglobulin free light chains
Etiology and Risk factors

- Etiology mostly unknown
- Aging immune system
- Rarely, Familial clustering
- Benzene, Radiation, Sheet metal work, Agent Orange
- Chronic inflammatory disorders – MGUS commonly seen
Myeloma Survival: Not curative, but treatable

- Median OS 6-10 years

Pulte et al, Leukemia/Lymphoma; 2014
Updated IMWG Criteria for Diagnosis of Multiple Myeloma

**MGUS**
- M protein < 3 g/dL
- Clonal plasma cells in BM < 10%
- No myeloma defining events

**Smoldering Myeloma**
- M protein ≥ 3 g/dL (serum) or ≥ 500 mg/24 hrs (urine)
- Clonal plasma cells in BM ≥ 10% to 60%
- No myeloma defining events
- Require advanced imaging to evaluate for bone disease

**Multiple Myeloma**
- Underlying plasma cell proliferative disorder
- AND 1 or more myeloma defining events
- ≥ 1 CRAB* feature
- Clonal plasma cells in BM ≥ 60%
- Serum free light chain ratio ≥ 100
- > 1 bone focal lesion with advanced imaging

*C*: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
*R*: Renal insufficiency (creatinine clearance < 40 mL/min or serum creatinine > 2 mg/dL)
*A*: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
*B*: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET-CT)

Rouleaux: stacked coins (RBCs) from protein binding
Soft Tissue Plasmacytomas (collections of plasma cells)
Natural History of Multiple Myeloma: Pts Experience Relapse

Asymptomatic

Symptomatic

MGUS or smoldering myeloma

ACTIVE MYELOMA

Plateau remission

First-line therapy

Second-line

Third-line

1. RELAPSE

2. RELAPSE

REFRACTORY RELAPSE

Durie BGM. Concise review of the disease and treatment options. Multiple myeloma; 2008/2009
Available from: http://myeloma.org/pdfs/cr08-eng_f1web.pdf
Myeloma Treatment Paradigm

Diagnosis and Risk Stratification

Induction followed by continuous therapy

Induction
Consolidation
Maintenance

Tumor Burden
Goals of Induction Therapy

- High response rate; rapid/deep response
- Improve performance status and quality of life
Figure 1: Milestones in MM treatment

Weijuan Li et al. Circulation. 2016;133:908-912
Treatments for Multiple Myeloma

1. Immunomodulatory Drugs:
   a. Thalidomide (Thalomid)
   b. Lenalidomide (Revlimid)
   c. Pomalidomide (Pomalyst) – Approved 2013

2. Proteasome Inhibitors:
   a. Bortezomib (Velcade)
   b. Carfilzomib (Kyprolis) – Approved 2013
   c. Ixazomib (Ninlaro) – Approved 2015
Treatments for Multiple Myeloma

3. Monoclonal Antibodies
   a. Daratumumab (Darzalex) – Approved 2015
   b. Elotuzumab (Empliciti) – Approved 2015

4. Histone Deacetylase Inhibitors
   a. Panobinostat – Approved 2015

5. Alkylators
   a. Cyclophosphamide (Cytoxan)
   b. Melphalan
   c. Bendamustine
IMiDs bind to the protein cereblon (CRBN), which activates the enzymatic activity of the CRBN E3 ubiquitin ligase complex.

The transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) are modified with ubiquitin (Ub) molecules, targeting them for proteolysis.

This alters the function of T cells and B cells, with a toxic outcome for multiple myeloma cells.
Elotuzumab is anti-SLAMF7 (CS1) and uses NK cells to kill myeloma

- Elotuzumab is a humanized IgG1 monoclonal antibody that recognizes SLAMF7 (CS1)

- SLAMF7 is a protein highly expressed by myeloma and natural killer (NK) cells

- Elotuzumab causes myeloma cell death via a dual mechanism of action
  - Directly activating NK cells
  - ADCC

SLAMF7- Signaling Lymphocyte Activation Molecule Family member 7
ADCC- antibody dependent cell-mediated cytotoxicity

Daratumumab is anti-CD38

IgG1κ human monoclonal antibody against CD38

The Proteasome

20S proteasome

Core particle
4-stacked rings
Large - 700 kilodaltons
Cleave between 2 pairs of AA

26S proteasome

Combines with 19S regulatory complex + ATP
Ubiquitin-marked protein receptor

19S + ATP
Proteasome Inhibition

Plasma cell apoptosis via impaired:
- DNA repair
- Cell-cycle control
- Abnormal protein configuration
- Cell signaling of NF-κB

Adapted from Adams J. Cancer Cell. 2004
Important balance between protein synthesis and degradation in the myocardium

Figure 1. Association of the Development of Cardiac Atrophy and Hypertrophy with Changes in the Balance between Protein Synthesis and Protein Degradation.

The development of cardiac atrophy involves both the inhibition of protein synthesis and a simultaneous increase in the rates of protein degradation (Panel A), resulting in shorter half-lives of individual cardiac proteins, as compared with the half-lives of proteins in a steady state, when protein synthesis and degradation are balanced (Panel B). The development of cardiac hypertrophy involves both an increased fractional synthesis rate of proteins and the suppression of protein degradation (Panel C), resulting in longer half-lives of cardiac proteins.² ³ ⁴ ⁵

Monte S. Willis, M.D., Ph.D., and Cam Patterson, M.D., M.B.A.
NEJM 2013;368:455-64.
**Cardiovascular Serious Events in Phase 3 Carfilzomib Trial**

- **ASPIRE Trial**
- **N=792: Car/Len/Dex vs Len/Dex**
- **Median OS 48.3 mo vs 40.4 mo (HR 0.79, p=0.005)**

### Table 3. Adverse Events in the Safety Population.*

<table>
<thead>
<tr>
<th>Event</th>
<th>Carfilzomib Group (N=392)</th>
<th>Control Group (N=389)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or Higher</td>
</tr>
<tr>
<td></td>
<td>number of patients (percent)</td>
<td>number of patients (percent)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>76 (19.4)</td>
<td>11 (2.8)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>56 (14.3)</td>
<td>17 (4.3)</td>
</tr>
<tr>
<td>Acute renal failure†</td>
<td>33 (8.4)</td>
<td>13 (3.3)</td>
</tr>
<tr>
<td>Cardiac failure‡</td>
<td>25 (6.4)</td>
<td>15 (3.8)</td>
</tr>
<tr>
<td>Ischemic heart disease§</td>
<td>23 (5.9)</td>
<td>13 (3.3)</td>
</tr>
</tbody>
</table>

| Total Cardiac AEs            | 26.6%                     | 11.4%                 | 15.6%     | 5.7%            |
| Total Cardiac AEs + Dyspnea  | 46%                       | 14.2%                 | 30.5%     | 7.5%            |
| DVT/PE                       | 10.2%                     |                       | 6.2%      |                 |

Stewart, AK et al, NEJM 2015, p.142-152.
Prospective Study of Cardiac Events during Proteasome Inhibitor Therapy for Relapsed Multiple Myeloma (PROTECT)

R. Frank Cornell, MD, MS, Bonnie Ky, MD, Brendan M Weiss, MD, Cherie Dahm, MD, Deepak K Gupta, MD, Liping Du, PhD, Joseph R Carver, MD, Adam D. Cohen, MD, Brian G Engelhardt, MD, Alfred L. Garfall, MD, Stacey A Goodman, MD, Shelton Lacy Harrell, MSN, Adetola A. Kassim, MD, MS, Trafina Jadhav, PhD, Madan Jagasia, MD, MBBS, MS, Javid Moslehi, MD, Rupal O’Quinn, MD, Michael R. Savona, MD, David Slosky, MD, Amanda Smith, Edward A. Stadtmauer, MD, FAC, Dan T. Vogl, MD, Adam Waxman, MD and Daniel Lenihan, MD

1Department of Medicine, Division of Hematology/Oncology, Vanderbilt University Medical Center, Nashville, TN; 2Department of Medicine, Division of Cardiovascular Medicine, University of Pennsylvania, Philadelphia, PA; 3Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; 4Department of Medicine, Division of Cardiovascular Medicine, Vanderbilt University Medical Center, Nashville, TN; 5Quantitative Sciences and Biostatistics, Vanderbilt University Medical Center, Nashville, TN; 6Department of Medicine, Division of Cardiovascular Medicine, Washington University, St. Louis, MO.
Screened for eligibility

Eligible and enrolled (n=95)

Received carfilzomib (n=65)

Monitored for CVAE

CVAE occurred (n=33)

No CVAE occurred (n=32)

Received bortezomib (n=30)

Monitored for CVAE

CVAE occurred (n=5)

No CVAE occurred (n=25)
<table>
<thead>
<tr>
<th>Cardiovascular Adverse Events</th>
<th>Carfilzomib Cardiovascular Events (n=56)</th>
<th>Bortezomib Cardiovascular Events (n=8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>12 (21%)</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>11 (20%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>23 (41%)</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Cardiac Chest Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>8 (14%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>9 (16%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>NA</td>
<td>2 (26%)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>13 (23%)</td>
<td>2 (26%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>13 (23%)</td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>2 (3.5%)(^1)</td>
<td>1 (13%)(^3)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>2 (3.5%)(^2)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>4 (7%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Acute Coronary Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 5</td>
<td>1 (2%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pulmonary Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>2 (3.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>2 (3.5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>4 (7%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Venous Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>0 (0%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>0 (0%)</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grades 1 and 2</td>
<td>25 (44%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Grade 3, 4 and 5</td>
<td>31 (56%)</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>All Grades</td>
<td>56 (100%)</td>
<td>8 (100%)</td>
</tr>
</tbody>
</table>
Cumulative incidence curves for time to first cardiac event

<table>
<thead>
<tr>
<th>n at risk</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>carfilzomib, any cardiac event</td>
<td>65</td>
<td>39</td>
<td>27</td>
<td>27</td>
<td>26</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>carfilzomib, CHF</td>
<td>65</td>
<td>51</td>
<td>41</td>
<td>40</td>
<td>36</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>bortezomib, any cardiac event</td>
<td>30</td>
<td>26</td>
<td>23</td>
<td>23</td>
<td>21</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>bortezomib, CHF</td>
<td>30</td>
<td>29</td>
<td>26</td>
<td>26</td>
<td>22</td>
<td>20</td>
<td>17</td>
</tr>
</tbody>
</table>
# BNP and NT proBNP are highly predictive of CVAEs

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cardiac Event (Yes)</th>
<th>Cardiac Event (No)</th>
<th>OR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline BNP or NT proBNP above normal at baseline</td>
<td>64%</td>
<td>18%</td>
<td>7.39 (2.9-19.2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BNP or NT proBNP increased above normal at week 2 or 3 during cycle 1</td>
<td>53%</td>
<td>2%</td>
<td>63.5 (7.39-509)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
## Multivariate Analysis

<table>
<thead>
<tr>
<th>Effect</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carfilzomib vs Bortezomib</td>
<td>3.0 (1.1 to 8.4)</td>
<td>0.04</td>
</tr>
<tr>
<td>Elevated baseline natriuretic peptide levels vs. normal levels</td>
<td>4.1 (2.1 to 8.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Normal baseline natriuretic peptide levels which became elevated mid-first cycle of treatment vs. normal levels</td>
<td>9.5 (4.3 to 20.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤1 traditional CV risk factors vs. ≥2</td>
<td>0.5 (0.3 to 0.9)</td>
<td>0.02</td>
</tr>
<tr>
<td>Time from myeloma diagnosis to enrollment onto PROTECT</td>
<td>0.98 (0.6 to 1.5)</td>
<td>0.9</td>
</tr>
</tbody>
</table>
Survival outcomes according to proteasome inhibitors (Figures A and B) and survival outcomes according to occurrence of cardiovascular event vs no cardiovascular event (Figures C and D)
Conclusions

• This is the first prospective study designed to systematically evaluate cardiac events in patients receiving carfilzomib or bortezomib

• CAEs were more common with carfilzomib than with bortezomib but usually did not require discontinuation of therapy with careful management

• Additionally, prospective monitoring with natriuretic peptides and detailed cardiac history to determine risk factors are useful in identifying patients at high risk of CAEs during PI treatment

• Closer cardiac monitoring with carfilzomib should be considered early into treatment since the majority of events occurred within the first 3 months of treatment initiation
Thromboembolic events are common in patients with myeloma

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>VTE Incidence Without Thromboprophylaxis, %</th>
<th>VTE Incidence With Thromboprophylaxis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>2–10</td>
<td>NA</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>2–26</td>
<td>8–25</td>
</tr>
<tr>
<td>Plus chemotherapy†</td>
<td>3–58</td>
<td>3–31</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>0–33</td>
<td>NA</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>8–75</td>
<td>3–14</td>
</tr>
<tr>
<td>Plus chemotherapy†</td>
<td>14</td>
<td>5–9</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alone</td>
<td>NA</td>
<td>2</td>
</tr>
<tr>
<td>Plus dexamethasone</td>
<td>NA</td>
<td>2–5</td>
</tr>
</tbody>
</table>

**Individual Risk Factors**
- Obesity (Body Mass Index ≥30)
- Previous VTE
- Central venous catheter
- Inherited thrombophilia
- Immobilization
- Surgery
- Cigarette smoking
- Co-morbidities:
  - Cardiac disease
  - Diabetes mellitus
  - Chronic renal disease
  - Acute infection

**Therapy-related Risk Factors**
- High-dose dexamethasone (≥480 mg/month)
- Concomitant use of erythropoietin
- Use of IMiDs (thalidomide, lenalidomide, or pomalidomide)
- Combination IMiDs with high-dose dexamethasone or doxorubicin or multiagent chemotherapy

**Myeloma-related Risk Factors**
- Disease Status
- Hyperviscosity

**Recommendations**
- Aspirin 81-325 mg once daily should only be recommended for low-risk patients (≤ 1 individual or myeloma-related risk factor)
- LMWH (equivalent of enoxaparin 40 mg once daily) or full-dose warfarin (target INR 2-3) should be recommended in the presence of ≥ 2 individual or myeloma-related risk factors
- LMWH or full-dose warfarin should be considered in all patients who receive high-dose dexamethasone or doxorubicin or multiagent chemotherapy, independent of the presence of additional risk factors
- The dose of LMWH should be adjusted according to renal function. LMWH is generally not recommended for patients with creatinine clearance < 30 ml/minute
- Thromboprophylaxis should be provided for the first 4 to 6 months of treatment, until disease control is achieved or as long as the risk of VTE remains high

Prospective Study of Apixaban for Primary Prevention of Venous Thromboembolism in Patients with Multiple Myeloma Receiving Immunomodulatory Therapy

R. Frank Cornell\textsuperscript{1}; Samuel Z Goldhaber\textsuperscript{2}; Brian G Engelhardt\textsuperscript{1}; Javid Moslehi\textsuperscript{3}; Madan Jagasia\textsuperscript{1}; Daryl Patton\textsuperscript{4}; Shelton Harrell\textsuperscript{1}; Robert Hall\textsuperscript{1}; Houston Wyatt\textsuperscript{1}; Gregory Piazza\textsuperscript{2}

\textsuperscript{1}Division of Hematology and Oncology, Department of Medicine, Vanderbilt University, Nashville, TN, USA; \textsuperscript{2}Division of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA; \textsuperscript{3}Cardio-Oncology Program, Vanderbilt University Medical Center, 2220 Pierce Ave, Nashville, TN; \textsuperscript{4}Vanderbilt Institute for Clinical and Translational Research
Patient Consent

All Inclusion Criteria Met
- Symptomatic Multiple Myeloma
- Planned IMiD Therapy
- ECOG Functional Status ≤ 2

No Exclusion Criteria Met

Intervention
Apixaban, 2.5 mg twice daily for 6 months

Primary Outcomes
Primary Safety Outcome
Major and Clinically-Relevant Non-Major Bleeding

Primary Efficacy Outcome
Symptomatic VTE
Bleeding Definitions

**Major bleeding:** overt bleeding that is associated with a decrease in hemoglobin of 2g/dL or more, requiring the transfusion of 2 or more units of blood, occurring in a critical site, or contributing to death

**Clinically relevant non-major bleeding:** overt bleeding that does not meeting the criteria for major bleeding, but is associated with medical intervention, surgical intervention, or interruption of the study drug
<table>
<thead>
<tr>
<th>Event</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>0</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>0</td>
</tr>
<tr>
<td>Clinically relevant non-major bleeding events*</td>
<td></td>
</tr>
<tr>
<td>Unprovoked epistaxis lasting &gt;5 min</td>
<td>1</td>
</tr>
<tr>
<td>Mechanical trauma</td>
<td>1</td>
</tr>
<tr>
<td>Arm ecchymoses</td>
<td>1</td>
</tr>
<tr>
<td>Superficial vein thrombosis</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction (MI)</td>
<td>0</td>
</tr>
<tr>
<td>Stroke or transient ischemic attack</td>
<td>0</td>
</tr>
<tr>
<td>Other event: Stopped apixaban early due to allergic reaction manifesting as generalized edema</td>
<td>1</td>
</tr>
</tbody>
</table>
Conclusions

• In this pilot study of 50 patients at 6-month analysis, low-dose apixaban was safe and well tolerated as thromboprophylaxis for patients with MM receiving IMiDs

• No patients experienced VTE, major hemorrhage, stroke, or MI

• Further randomized studies are needed to validate apixaban as a standard primary prevention anti-thrombotic strategy for patients with MM receiving IMiDs

• This treatment has the potential to greatly improve VTE prophylaxis options for patients with MM
Amyloidosis: A Systemic Disease with a Host of Complications, Particularly Cardiac
Über eine im Gehirn und Rückenmark des Menschen aufgefundene Substanz mit der chemischen Reaction der Cellulose.

Von Rud. Virchow.


Ich habe diese Untersuchung so oft und mit so vielfachen Vorsichtsmaß-
Amyloid History

- Animal substance giving a blue reaction with iodine, similar to plant starch
- Amyloid in Greek is "starch-like"
- Shortly found to be a protein, not starch, but "amyloid" has stuck.
- Later the Congo Red stain was developed (1884)
Green Birefringence in Polarized Light Shows Fibillary Nature of Amyloid Protein
Green Birefringence in Polarized Light Shows Fibillary Nature of Amyloid Protein
• These result from misfolding of a soluble protein resulting in beta-pleated sheet

• Accurate diagnosis is critical
Liquid Chromatography/Tandem Mass Spectrometry

Amyloid Fibrils

Trypsin

Tryptic Peptides

Fractionated Tryptic Peptides

trypsin

liquid chromatography

mass spectrometer

mass

compare all known proteins

result

fragment

mass spectrometer

mass
Classification

▪ Amyloidosis is not a single disease but a term for group of rare diseases that share a common feature of extracellular deposition of pathologic insoluble fibrillar proteins in organs and tissues which can lead to compromise of organ function and death

▪ Primary or AL: plasma cells releasing misfolded light chain (lambda>kappa) which becomes amyloidogenic
Organ Involvement in AL amyloidosis

AL amyloidosis

Improvement in survival in AL amyloidosis throughout 30 years

Plasma cells

Misfolded monoclonal light chain

Heart 74%
CHF 47%
Kidney 65%
Nephrotic s. 42%
Renal failure 45%
Liver 17%
GI 8%
Soft tissues 17%
ANS 14%
PNS 15%

2005-2008 (352 patients)
2000-2004 (418 patients)
1995-1999 (208 patients)
1984-1994 (153 patients)
p = 0.016

Time (months)
Clinical Features

- 3000 new cases/year in US; Median survival of 3 years
- Light chain producing conditions: MGUS, smoldering myeloma, myeloma, Waldenstrom’s macroglobulinemia.
- Symptoms a median of 2 years before dx
- Nephrotic range proteinuria, unexplained non-ischemic cardiomyopathy, peripheral neuropathy, macroglossia, periorbital purpura (raccoon eyes), bleeding diathesis (factor X deficiency)
Score of 1 for 3 prognostic variables (cTnT $\geq 0.025$ ng/ml, NT-proBNP $\geq 1800$ pg/ml, FLC diff $\geq 18$ mg/dl) Stages I, II, III, IV

Kumar et al, JCO, 2011
AL Amyloidosis Treatment

- Supportive Care
- Chemotherapy (Melphalan-Prednisone; Bortezomib, Cyclophosphamide; Ixazomib; Pomalidomide)
- Immunotherapy: Daratumumab
- Autologous Stem Cell transplant (ASCT)
- Solid organ transplant
- Investigational-emerging therapies
Medical Management

- Medical management of the involved organs:
  - RAAS blockade for proteinuria
  - Dialysis for renal failure
  - Management of cardiomyopathy
  - ICD/Pacer
  - Neuropathic pain meds for neuropathy
  - Gastric motility agents autonomic dysfunction
ASCT vs Chemo Alone

- 81 pt (CT n=38; ASCT n=43)
- OS of 64 mo vs. 15 mo p=0.03
- Improved OS with ASCT (HR 4.78, 95% CI 1.45-15.8, P=0.01)

Cornell et al, BBMT, 2017 Sep;23(9):1473-1477
6 Minute Walk Test

- Can 6MWT be used as a functional measure to compliment biochemical response in patients with AL cardiac involvement?
- 22 patient with cardiac AL treated with bortezomib-based chemotherapy
- 45% chemotherapy and 55% chemotherapy then ASCT
- 6MWT at baseline and end of planning therapy
- Median follow-up 2.15 years
Results

- 59% cardiac stage I/II; 41% stage III/IV
- Median increase of 26.5% or 90 meters in 6MWT distance
- 81% (n=18) improved, 9% (n=2) decreased, 9% (n=2) stable
- Improvements associated with improved BNP, LV EF, troponin I, NYHA class and cardiac response (p<0.001)
- Multivariate: Cardiac response (BNP decrease of 30% or NYHA class decrease ≥ 2) had median increase of 190 meters

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Best Practices in the Treatment of Patients With Multiple Myeloma

Change in 6MWT Distance (meters)

Cardiac Response

No Cardiac Response

p = 0.004
AL Amyloidosis Treatment: Key Points

- Rapidly reduce the supply of monoclonal light chain by suppressing the underlying plasma cell clone
- Maximize medical management and supportive care to sustain the function of organs involved and improve QOL
- Hematologic response, degree of response and degree of cardiac involvement are the most important predictors of survival