Objectives

1. Provide an overview of the types and spectrum of multiple myeloma, including MGUS
2. Review the diagnosis and staging of myeloma, with emphasis on risk stratification
3. Discuss the overall approach to therapy
4. Highlight the improvement in prognosis for patients with myeloma
5. Outline the basics of AL amyloidosis and its outcomes
Multiple myeloma

- Second most common hematological malignancy
- Survival has improved (8 vs. 3 yrs) with ongoing improvement
- 20% of Patients still survive < 2 yrs (high risk disease)
- Remains largely incurable

American Cancer Society. Cancer Facts & Figures 2011

Immunoglobulins

- Antigen binding sites
- Variable region on heavy chain
- Light chain
- Disulfide bridges
- Heavy chain
- Constant region on light chain
- Variable region on light chain
- Constant region on heavy chain
Molecular progression

Normal plasma cell → MGUS → Asymptomatic Myeloma → Active Myeloma → Aggressive Myeloma

- Translocations
- Infection
- Immunization
- ras & p53 mutation
- c-myc dysregulation
- Bone resorption
- Angiogenesis
- Del 13
- Secondary translocations

The Spectrum of Myeloma

<table>
<thead>
<tr>
<th></th>
<th>MGUS</th>
<th>Asymptomatic MM (smoldering)</th>
<th>“True” MM</th>
<th>PC Leukemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organ damage</td>
<td>none</td>
<td>none</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Marrow Disease</td>
<td>&lt;10% plasma cells</td>
<td>≥ 10% plasma cells</td>
<td>≥ 10% plasma cells</td>
<td>Plasma cells in blood</td>
</tr>
<tr>
<td>Management</td>
<td>Monitor 1-2 times/yr</td>
<td>Close follow up (q 3 mts)</td>
<td>therapy</td>
<td>Highdose combo chemo</td>
</tr>
<tr>
<td>Transformation rate</td>
<td>1%/yr</td>
<td>10-20%/yr</td>
<td>n/a</td>
<td>n/a</td>
</tr>
</tbody>
</table>
Multiple Myeloma - Types

- Subtypes of MM are determined based on the kind of abnormal protein
  - IgG – 55%
  - IgA – 25%
  - IgD – 1-2%
  - IgM – 1%
- Light Chain Disease only – 20%
- Non Secretors 1-2 %
Multiple Myeloma

• Unfortunately, MM is not a curable disease (yet!!)
• Historically most people did not live for much more than 2 years...
• However, the average survival is now at least 8 years
  • This has been a result of two key developments:
    1. Autologous Stem Cell Transplant
    2. Novel Drugs (thalidomide, bortezomib, lenalidomide)

Multiple Myeloma - Epidemiology

• Incidence
  • It is a rare condition, occurring in about 4 people per 100,000 (1% of all cancers)
  • About 21000 new cases this year
• It is more common in men than women
• It is more common in the black population
• Average age of diagnosis is 65
  • Less than 10% of cases occur in patients <50
  • Less than 2% of cases occur in patients <40
Multiple Myeloma – Causes?

• The cause of myeloma is still unknown
• Some have suggested:
  • Radiation, chemicals (benzenes), herbicides and insecticides
  • Genetics or even viruses
• Familial Myeloma – still rare
• However, nothing is conclusive, and it is likely a combination of many factors...

Myeloma Staging

• Older system of Salmon-Durie staging
  • Not as useful anymore
• Newer system of using 2 factors:
  • Albumin and Beta-2-microglobulin
  • It is “prognostic” for survival
• Practically, there are 2 stages
  1. Can wait and watch
  2. Requires treatment
## International Staging System for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival</th>
</tr>
</thead>
</table>
| I     | Serum $\beta_2M < 3.5$ mg/L  
Serum albumin $\geq 3.5$ g/dL | 62 mo |
| II    | Serum $\beta_2M < 3.5$ mg/L  
Serum albumin $< 3.5$ g/dL  
OR  
Serum $\beta_2M$ 3.5 to $< 5.5$ mg/L* | 44 mo |
| III   | Serum $\beta_2M \geq 5.5$ mg/L | 29 mo |

*Irrespective of serum albumin level


## ISS: Survival

<table>
<thead>
<tr>
<th>Stage</th>
<th>Deaths/N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>606/1111</td>
<td>62 (58,65)</td>
</tr>
<tr>
<td>II</td>
<td>1544/1505</td>
<td>44 (42,45)</td>
</tr>
<tr>
<td>III</td>
<td>988/1305</td>
<td>29 (25,32)</td>
</tr>
</tbody>
</table>

Cytogenetics

- These are the genes of the plasma cells
- May indicate more about the biology of the disease
- Most can be found at diagnosis, but others may be “acquired” later
- Could well be the most “prognostic” tool in myeloma as it may separate “high risk” myeloma from standard risk

Molecular Prognostic Model

- t(4;14)
- t(14;16)
- -17p13
- All others including t(11;14)  
  - Poor 24.7 mos
  - Intermediate 42.3 mos
  - Good 51.0 mos

Risk “Stratification”

- We have come to learn that myeloma is really many diseases in one
- Can be thought of as “slow growers” and “fast growers”
- High risk disease in about 25%
  - Mostly defined by certain cytogenetics
    - p53 deletion (=loss of 17p)
    - Translocations: 4;14, 14;16
  - Other markers...
  - More likely to relapse more quickly, likely need more aggressive and continuous therapy

mSMART

*Mayo Stratification for Myeloma And Risk-adapted Therapy*

Newly Diagnosed Myeloma

*Website: www.msmart.org*

### mSMART: Classification of Active MM

#### mSMART 2.0: Classification of Active MM

<table>
<thead>
<tr>
<th></th>
<th>High-Risk 20%</th>
<th>Intermediate-Risk 20%</th>
<th>Standard-Risk 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FISH</strong></td>
<td>Del 17p</td>
<td>t(4;14)*</td>
<td>Hyperdiploid</td>
</tr>
<tr>
<td></td>
<td>t(14;16)</td>
<td>PCLI ≥3%</td>
<td>t(11;14)</td>
</tr>
<tr>
<td></td>
<td>t(14;20)</td>
<td></td>
<td>t(6;14)</td>
</tr>
<tr>
<td><strong>GEP</strong></td>
<td>High risk signature</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetic</strong></td>
<td>Deletion 13 or hypodiploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PCLI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 years | 4-5 years | 8-10 years
**mSMART – Off-Study**

**Transplant Eligible**

**High Risk**
- VRD x 4
- ASCT, especially if not in CR
- VRD maintenance for minimum of 1 year

**Intermediate Risk**
- Induction with CyBorD
- Autologous stem cell transplant (ASCT)
- Bortezomib based consolidation for minimum of 1 year

**Standard Risk**
- 4 cycles of Rd or CyBorD
- Collect Stem Cells
- Autologous stem cell transplant (ASCT)
- Continue Rd

* Bortezomib containing regimens preferred in renal failure or if rapid response needed

† Continuing Rd is option for patients responding to Rd and with low toxicities; Dex is usually discontinued after first year

‡ Len maintenance may be less helpful for patients who have received len induction

**mSMART – Off-Study**

**Transplant Ineligible**

**High Risk**
- VRD*

**Intermediate Risk**
- MP + weekly Bortezomib** or weekly CyBorD
- Bortezomib maintenance

**Standard Risk**
- Rd#
- Observation

* In patients in whom administration of thalidomide or bortezomib is of concern, consider MP or Rd

† Continuing Rd is an option for patients responding well to induction with low toxicities; Dex is usually discontinued after first year

‡ Bortezomib containing regimens preferred in renal failure or if rapid response needed

*Clinical trials strongly recommended as the first option

Dr. Joe’s Summary of Transplant

- ASCT still remains standard of care in eligible patients
- WHO – offer to all, be realistic in pts with high risk disease
- WHAT – single ASCT, reserve allo for VERY FEW (young, high risk, rapid progression)
- WHEN – ideally after induction, but may delay is well and in VGPR or greater
- AGAIN – if PFS more than 2 years and tolerated 1st well

Maintenance Therapy

- Past with thalidomide and others
- Maintenance vs consolidation
- Lenalidomide maintenance
  - High dose therapy and ASCT
    - CALGB 100104
    - IFM 05
  - Transplant ineligible patients
    - MM 015 study
Maintenance Therapy - CALGB Trial

568 patients enrolled

Patients achieving Stable disease or better after any induction therapy randomized between day 100-110 (n=460)

Lenalidomide 10 mg/day with aim to reach 15 mg/day

Till progression

Placebo

McCarthy et al NEJM. May 10, 2012

Maintenance Therapy - IFM

614 patients enrolled with in 6 months of HDT provided no PD

Lenalidomide 25 mg day 1-21 q 28 days for 2 cycles

Lenalidomide 10 mg/day with aim to reach 15 mg/day

Till progression

Placebo

Attal et al NEJM. May 10, 2012
### Efficacy of Maintenance

<table>
<thead>
<tr>
<th></th>
<th>CALGB trial</th>
<th>IFM trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP (months)</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>3 yr. OS (%)</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP (months)</td>
<td>39</td>
<td>41</td>
</tr>
<tr>
<td>3 yr. OS (%)</td>
<td>88</td>
<td>84</td>
</tr>
</tbody>
</table>

*McCarthy et al. And Attal et al NEJM. May 10, 2012*

### Toxicity of Maintenance

<table>
<thead>
<tr>
<th></th>
<th>CALGB trial</th>
<th>IFM trial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III/IV hematological:</td>
<td>17</td>
<td>22</td>
</tr>
<tr>
<td>SPM (n)</td>
<td>6</td>
<td>18</td>
</tr>
<tr>
<td><strong>Lenalidomide</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade III/IV hematological:</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>SPM (n)</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

*McCarthy et al. And Attal et al NEJM. May 10, 2012*
Dr. Joe’s Conclusions

- First do no harm
- Consider QOL and AEs
- PFS inadequate endpoint for maintenance study placebo vs active drug design
- Len maintenance not yet proved to be superior to salvage Len
- One immature, (weakly) positive study does not change practice esp. if 2nd more mature trial negative
- Don’t forget COST!

Dollar Cost of Regimens (BSA 2 m²)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Cost per 28 days (per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. VRD</td>
<td>$23,000 (276K)</td>
</tr>
<tr>
<td>2. VTD</td>
<td>$22,000 (264K)</td>
</tr>
<tr>
<td>3. PAD</td>
<td>$14,400* (173K)</td>
</tr>
<tr>
<td>4. VD</td>
<td>$13,800 (166K)</td>
</tr>
<tr>
<td>5. CyBorD (weekly)</td>
<td>$9,200 (110K)</td>
</tr>
<tr>
<td>6. Rd</td>
<td>$9,000 (108K)</td>
</tr>
<tr>
<td>7. TD</td>
<td>$8,200 (98K)</td>
</tr>
</tbody>
</table>

*add $4000 if Doxil
Single-Agent Activity of 39 Drugs Tested in Multiple Myeloma

Provided by Dr. Keith Stewart

Proteasome Inhibitors: MoA

β-subunit ring of the proteasome

Catalytic site

Three distinct N-terminal threonine protease active sites

<table>
<thead>
<tr>
<th>Type</th>
<th>Catalytic inhibition</th>
<th>Reversibility</th>
<th>PO/IV</th>
<th>Dosing (days/cycle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>Boronic</td>
<td>X</td>
<td>X</td>
<td>Reversible</td>
</tr>
<tr>
<td>Carfilzomib</td>
<td>Epoxiketone</td>
<td>X</td>
<td></td>
<td>Irreversible</td>
</tr>
<tr>
<td>MLN9078</td>
<td>Boronic</td>
<td>X</td>
<td>X</td>
<td>Reversible</td>
</tr>
<tr>
<td>Marizonib</td>
<td>X</td>
<td>X</td>
<td>x</td>
<td>Reversible</td>
</tr>
</tbody>
</table>

Bortezomib MLN9078

Carfilzomib CEP-18870
Carfilzomib

Carfilzomib is a new, selective and irreversible proteasome inhibitor with pre-clinical anti-tumor activity. Responses seen in Phase I Myeloma trials.

Tetrapeptide

Ketoepoxide

Responses in Bortezomib refractory IMiD exposed patients (Response-evaluable Population, N=257)

- ORR = 24%
- CBR = 34%
- DOR (≥ PR) and (≥ MR) = 8.3 mo

<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR*</td>
<td>1</td>
<td>0.4%</td>
</tr>
<tr>
<td>VGPR</td>
<td>13</td>
<td>5.1%</td>
</tr>
<tr>
<td>PR</td>
<td>48</td>
<td>18.7%</td>
</tr>
<tr>
<td>MR</td>
<td>26</td>
<td>10.1%</td>
</tr>
<tr>
<td>SD</td>
<td>89</td>
<td>34.6%</td>
</tr>
<tr>
<td>PD</td>
<td>69</td>
<td>26.8%</td>
</tr>
</tbody>
</table>
Neuropathy was infrequent and not dose limiting
Pooled data from single agent studies (003 / 004 / 005)

- Peripheral neuropathy occurred infrequently across all single agent studies.
  - Only 6 patients (1.2%) experienced a Grade 3 PN event
  - No Grade 4 PN events
- Only 1 patient had drug discontinued for PN (study 004; BTZ-treated arm)


Overall Survival

<table>
<thead>
<tr>
<th>N</th>
<th>Median (mo)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>257</td>
<td>15.5 months</td>
<td>12.7 – 19.0</td>
</tr>
</tbody>
</table>
Carfilzomib (Kyprolis) Summary

- Novel Proteasome inhibitor
  - Given IV twice weekly
  - Essentially no neuropathy
  - Minimal toxicity – tumor lysis, cardiac, pulmonary
- FDA approved July 2012
  - Previous exposure to IMID (thalidomide or lenalidomide) AND bortezomib, and relapsing

Molecular Structure of Thalidomide, Lenalidomide and Pomalidomide

- Thalidomide
  - 100-200 mg/d
  - Neuropathy
  - Constipation
  - Sedation
  - DVT
- Lenalidomide
  - 15-25 mg/d
  - Myelosuppression
  - Skin rash
  - DVT
- Pomalidomide
  - 1-4 mg/d

Structurally similar, but functionally different both qualitatively and quantitatively
Pomalidomide With Dex in Patients With MM Refractory to Novel Agents

Percent Response

- Len Refractory
  - CR: 8%
  - VGPR: 35%
- Thal Refractory
  - CR: 12%
  - VGPR: 25%
- Bz Refractory
  - CR: 10%
  - VGPR: 30%
- Bz & Len Refractory
  - CR: 20%
  - VGPR: 40%


Survival in MM

- 1965–1974
- 1975–1982
- 1983–1995
- 1996–2004

Alexanian A et al. M. D. Anderson historical MM patient survival data (unpublished)
Myeloma Survival: All Ages
SEER Program, 1980-2007

SUBJECTS:
Newly diagnosed (incident) cases of Myeloma diagnosed in 9 core areas of the SEER Program during the time period 1980-2007

NUMBER OF SUBJECTS:
Diagnosed 1980-89: 7901 (48.82 % alive after 3 years)
Diagnosed 1990-99: 9353 (50.56 % alive after 3 years)
Diagnosed 2000-2007: 8300 (57.64 % alive after 3 years)

Total subjects = 25,554
P-Value: <0.0001
Survival outcomes in elderly patients with plasma cell myeloma: The three-decade Eastern Cooperative Oncology Group (ECOG) experience

- Most of the survival benefit is seen in <65
- Analyzed 4 Phase 3 clinical trials (ASCT excluded)
- Three cohorts:
  - A 1988-1993
  - B 1994-2000
  - C 2001-2006

---

<table>
<thead>
<tr>
<th>Accrual period</th>
<th>Pts &lt;65 yr</th>
<th>No.</th>
<th>Median OS (0.95 CI) [yr]</th>
<th>Pts ≥65 yr</th>
<th>No.</th>
<th>Median OS (0.95 CI) [yr]</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 1988-1993</td>
<td>371</td>
<td>3.7 (3.4, 4.1)</td>
<td>282</td>
<td>3.3 (2.9, 3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B 1994-2000</td>
<td>100</td>
<td>3.5 (2.9, 4.1)</td>
<td>93</td>
<td>3.0 (2.6, 3.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 2001-2006</td>
<td>330</td>
<td>7.4 (6.2, NA)*</td>
<td>352</td>
<td>3.7 (3.3, 4.9)**</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Comparing C to A+B, p<.001 ** Comparing C to A+B, p=.012
Conclusions - Myeloma

- Myeloma treatment must be tailored to the individual patient – based on both patient and disease factors
- Stem cell transplant is still the standard of care in eligible patients
- Prognosis is very much based on risk stratification
- Long term prognosis has dramatically improved in last decade
Adventures in Amyloid

Objectives

1. Provide an overview of the pathophysiology of amyloidosis
2. Outline the types of amyloidosis with emphasis on AL, AL and ATTR
3. Review the importance of accurate diagnosis
4. Discuss the clinical features and organ involvement of amyloidosis
5. Highlight the approach to therapy of amyloidosis
Amyloidosis - General

- Amyloid = “starch-like”, term originally coined by R. Virchow
- Amyloidosis = protein misfolding disorder
- Extracellular deposits of abnormally folded protein with:
  1. Ultrastructural appearance
     Fibrils with antiparallel beta-pleated sheet configuration on X-ray diffraction
  2. Common staining properties
     Congo Red staining (leading to green birefringence to polarized microscopy) & use of Thioflavine T

Amyloid Deposition

- Pattern:
  - Abnormal protein is elevated and triggers a cascade
  - Interacts with immune system to yield amyloid
  - Amyloid is deposited in various organs

Importance of “precursor” protein to form fibrils
- Immunoglobulin Light chains in AL
- Serum amyloid A protein in AA
- Transthyretin in ATTR

There are over 30 types of amyloidosis identified
### Diversity of Amyloidosis

<table>
<thead>
<tr>
<th>Amyloid Protein</th>
<th>Precursor</th>
<th>Type or Variant</th>
<th>Clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>kappa, lambda</td>
<td>Ak, Al</td>
<td>PCD, Myeloma-associated Reactive (2°)</td>
</tr>
<tr>
<td>AA</td>
<td>apo SAA</td>
<td>Met 30, Met 111</td>
<td>EMF, PAN</td>
</tr>
<tr>
<td>ATTR</td>
<td>transthyretin</td>
<td>Met 111</td>
<td>FAP(Scrapie)</td>
</tr>
<tr>
<td>ATTR</td>
<td>transthyretin</td>
<td>Met 30</td>
<td>FAP(Finnish)</td>
</tr>
<tr>
<td>ATTR</td>
<td>transthyretin</td>
<td>Ile 122</td>
<td>SSA, AD</td>
</tr>
<tr>
<td>AapoI</td>
<td>apo A1</td>
<td>Arg 26</td>
<td>FAP(Iwao)</td>
</tr>
<tr>
<td>AGel</td>
<td>gelsolin</td>
<td>Asn187</td>
<td>FAP(Finnish)</td>
</tr>
<tr>
<td>AB</td>
<td>B protein precursor</td>
<td>Gln 618</td>
<td>chronic dialysis, Down’s syndrome, HGHW, Dutch, HCHWA, Icelandic</td>
</tr>
<tr>
<td>ACys</td>
<td>Cystatin C</td>
<td>Gln 68</td>
<td>AD</td>
</tr>
<tr>
<td>APBP</td>
<td>PBP</td>
<td>PrPsc, PrPscD</td>
<td>CJD (Creutzfeldt-Jakob disease), Kuru, Scrapie</td>
</tr>
<tr>
<td>ACal</td>
<td>(Pro)calcitonin</td>
<td>(Pro)calcitonin</td>
<td>GSS (Gerstmann-Straussler-Scheinker syndrome)</td>
</tr>
<tr>
<td>AANF</td>
<td>atrial natriuretic factor</td>
<td></td>
<td>isolated atrial amyloidosis</td>
</tr>
<tr>
<td>AIAPP</td>
<td>islet amyloid polyepitope</td>
<td></td>
<td>diabetes type II, insulinoma(islet of Langerhans)</td>
</tr>
</tbody>
</table>

### Nomenclature

- **Old:**
  - Primary Amyloidosis
  - Secondary Amyloidosis
  - Hereditary Amyloidosis

- **New:**
  - AL
  - AA
  - ATTR (and other hereditary types)
Take Home Point #1

- Amyloidosis is triggered by an abnormal precursor protein

A Pathological Diagnosis

- Although the disease may be suspected on clinical grounds, it must be confirmed by pathology
- Tissue is the issue
- Specific to disease is that the protein deposits stain positive for Congo Red
Biopsy Required

• General approach is to pursue least invasive or symptom/sign directed biopsy

• Fat aspirate – low risk, convenient, sensitivity of 75%

• Bone Marrow – low risk, but low sensitivity (50-60%)

• Gingival Bx – less common now, some pain, sensitivity around 65%

• Organ directed:
  • Kidney, heart, nerve, liver…
Subtyping

• Just proving Congo Red positivity is not sufficient
• Subtyping (AL, AA, ATTR…. ) is critical but can be challenging
• Staining may be helpful, especially when clinical picture not clear
• “gold” standard is mass spectroscopy

Take Home Point #2

• Amyloidosis is a clinico-pathological disease that requires accurate biopsy
AA Amyloidosis

- Worldwide the most common form of amyloidosis
- Trigger protein is serum amyloid A (family of CRP)
- Due to longstanding inflammation
  - World: TB, FMF, Chronic infections
  - North Am: RA, IBD...
- Does not present with cardiac involvement
- Key to therapy is control of inflammation
ATTR Amyloidosis

- Most common form of hereditary amyloid
- Precursor protein is an ABNORMAL form of transthyretin (produced in liver)
- Must keenly take a family history
- Genetic testing required
- In eligible patients, treatment is liver transplant
- Underscores the need for accurate diagnosis

“Senile” Amyloid

- Perhaps most common form as likely underdiagnosed
- Precursor is NORMAL transthyretin (ie wild type)
- Most common in elderly patients
- Primarily manifest in heart with arrhythmias or progressive diastolic dysfunction
- Hallmark is that is very slow, treatment is usual cardiac management (meds, pacer...)
AL Amyloidosis

- Most common form of amyloidosis in North America
- Due to deposition of protein derived from immunoglobulin light chain fragments
- Plasma cell dyscrasia associated with monoclonal protein production
- Can occur alone or in combination with Multiple Myeloma or Waldenstrom’s macroglobulinemia
- Similar to immunoglobulin deposition disease – key difference is protein folding to form fibrils or include amyloid cofactors

AL – The Diagnostic Dilemma

- NO one symptom or sign defines the disease
- Clinical presentation is widely variable
- Most common
  - Proteinuria (NYD)
  - Neuropathy
  - Diastolic dysfunction
  - MGUS
AL Amyloidosis

- Need to clearly identify monoclonal origin
  - Bone marrow findings
  - Protein in Serum or Urine
  - Role of serum free light chain assay
- Still requires pathological confirmation
- Important distinction of localized vs systemic disease

Localized vs Systemic

- The process may occur in a general systemic way, or in a very localized way
- Some types of amyloid are always localized (incl Alzheimers, Prion...)
- Most are primarily systemic, but may also be localized (AL, AA, ATTR)
Take Home Point #3

• Distinguishing between localized and systemic amyloidosis is crucial to appropriate treatment

Myeloma vs AL Amyloidosis

• Both are diseases of the plasma cell
• Although independent, they can co-exist
  • If so, there is one that is “dominant”
  • Le more like myeloma: anemia, bony disease, kidney failure
  • Le more like amyloid: weakness, protein in urine, heart involvement…
• Historically treatments are rather similar
• Amyloidosis is likely 10 times less common
AL Amyloidosis – Organ Involvement

- Kidney...proteinuria, then renal dysfunction
- Heart...restrictive CM, wide septum, low BP, arrhythmia (usually tachy), elevated Troponin, NT-pro-BNP
- Nerves
  - autonomic (low blood pressure, dizziness, balance)
  - Peripheral (numbness, tingling)
- GI...upper gi bleeding, gastroparesis or chronic diarrhea
- Liver...hepatomegaly, high ALP
- Skin...easy bruising, amyloidomas, macroglossia
- Blood...acquired FX deficiency
- Other: thyroid, lung, bladder, eye...
AMYLOIDOSIS: PROTEIN MISFOLDING DISEASE

Small dangerous plasma cell clone
Median bone marrow plasma cell: 7%
fewer chromosomal aberrations compared with MM

75% λ
25% κ

Early diagnosis is vital in AL amyloidosis

<table>
<thead>
<tr>
<th>Organ or syndrome</th>
<th>present in</th>
<th>Early “red flags”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>70%</td>
<td>NT-proBNP &gt;332 ng/L (100% sensitivity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BNP &gt;73 ng/L (89% sensitivity)</td>
</tr>
<tr>
<td>Kidney</td>
<td>70%</td>
<td>Urinary albumin &gt; 0.5 g/day</td>
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<tr>
<td></td>
<td></td>
<td>eGFR &lt;50 mL/min per 1.73 m²</td>
</tr>
<tr>
<td>Liver</td>
<td>22%</td>
<td>Elevation of ALP or γ GT in absence of other causes</td>
</tr>
<tr>
<td>PNS-ANS</td>
<td>14%</td>
<td>Neuropathic pain and loss of sensitivity to temperature</td>
</tr>
<tr>
<td>Progressive sensory-motor neuropathy</td>
<td></td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Soft tissues</td>
<td>13%</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Purpura (peri orbital)</td>
<td></td>
<td></td>
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<tr>
<td>Macroglossia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscular pseudohypertr.</td>
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</tbody>
</table>
## AL Amyloidosis Therapy

- Under 70ish, good cardiac function
  - Autologous Stem Cell Transplant
- Not candidate for ASCT
  - Cytoxan, Bortezomib, Dexamethason (CYBORD)
  - Melphalan & Dexamethasone (Palladini)
  - Mel & Pred
- Relapsed disease
  - Clinical trials!
  - Thalidomide (poorly tolerated)
  - Lenalidomide (revlimid)
- Supportive Care for Low BP: florinef, midodrine

## Amyloid and BMT

- Associations with poor prognosis (ie DEATH):
  - Troponin >0.07
  - Repeated syncope
  - Intraventricular septum >15mm
  - SBP <90
  - Uncontrolled CHF
  - Dramatic CHF with collection
AL Amyloidosis

- Supportive Care
  - Cardiac
    - Low BP – midodrine or flrinef
    - Arrhythmia – possible amiodarone
  - Renal
    - Careful diet mgt, judicious use of ACE inhibition
  - GI
    - Symptomatic mgt of diarrhea or gastroparesis
  - Neuro
    - If painful, gabapentin or lyrica

Important Reminder

- This disease is usually diagnosed too late in its course
- Early identification by organ involvement
- Don’t for its connection to MGUS
- Not just a diagnosis in morning report
Conclusions – AL Amyloidosis

• Amyloidosis is a protein deposition characterized by congo red staining and a precursor protein

• AL amyloidosis is uncommon, but may be initially difficult to diagnose if not suspected

• Consider AL in unexplained proteinuria, heart failure, MGUS and neuropathy

• All patients with amyloidosis should be seen at a center of excellence