Plasma Cell Disorders
Subtypes of Plasma Cell Disorders

- Increased Plasma Cells
  - Monoclonal Gammopathy
  - Myeloma
  - Macroglobulinemia (IgM)

- Increased / Altered Products of Plasma Cells
  - Light Chain Amyloidosis
  - Light Chain Deposition Disease
B cell Development As a Framework for Malignancies

- Lymph node
  - Virgin B cell
  - Lymphoblast
  - Plasmablast
  - Lymphoplasmacyte
    - IgM
  - Switch Recombination
  - Somatic Hypermutation
- Bone Marrow
  - Plasma cell
  - Pre-B cell
  - V(D)J Recombination
  - G,A,E

**Diagram:**
- Germinal Center
  - Plasmablast
  - Switch Recombination
  - Somatic Hypermutation
  - Virgin B cell
  - Lymphoblast
  - IgM

**Key Terms:**
- Bone Marrow
- Lymph node
- Germinal Center
- Pre-B cell
- Plasma cell
- Virgin B cell
- Lymphoblast
- Plasmablast
- Lymphoplasmacyte
- IgM
- Switch Recombination
- Somatic Hypermutation
- G,A,E
- V(D)J Recombination
B cell Development As a Framework for Malignancies

Lymph node

Germinal Center

Plasmablast

SOMATIC HYPERMUTATION

WALDENSTROM’S

FOLLICULAR LYMPHOMA

Lymphoblast

BURKITT’S LYMPHOMA

Virgin B cell

CLL

Bone Marrow

MULTIPLE MYELOMA

Plasma cell

G,A,E

ALL

Pre-B cell
New Cases of Cancer in the United States (2013 estimates)\(^1\)

<table>
<thead>
<tr>
<th>Type of Cancer</th>
<th>Number of Cases (x1000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>69,740</td>
</tr>
<tr>
<td>Myeloma</td>
<td>22,350</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
<td>15,680</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>14,590</td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>9,290</td>
</tr>
<tr>
<td>Other leukemia</td>
<td>6,350</td>
</tr>
<tr>
<td>Acute lymphocytic leukemia</td>
<td>6,070</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>5,920</td>
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</tbody>
</table>
Clinical spectrum of clonal expansions of transformed plasma cells in patients

- Normal cell
- Transformed cell
- MGUS (premalignant)
- Multiple myeloma (malignant)

**Stable intramedullary expansion**
- Asymptomatic.

**Progressive intramedullary expansion**
- Anemia, bone pain, infections
- Lytic bone disease.
- Incurable, limited survival.

- 13000 deaths/yr in USA.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Distinctive Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma Cell Leukemia¹</td>
<td>Circulating plasma cells (PC) &gt; 2,000/uL if the leukocyte count exceeds 10,000/uL or 20% PC with lower leukocyte levels</td>
</tr>
<tr>
<td>Solitary Plasmacytoma²</td>
<td>Solitary bone or soft tissue lesion with evidence of clonal plasma cells, normal BM with no evidence of clonal plasma cells, normal skeletal survey, absence of end-organ damage</td>
</tr>
<tr>
<td>Waldenström’s Macroglobulinemia³</td>
<td>Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration</td>
</tr>
<tr>
<td>Light Chain Deposition Disease⁴</td>
<td>Characterized by deposition of monoclonal, amorphous light chains, predominantly kappa light chains. Histologic appearance can mimic AL-amyloidosis, However, unlike AL amyloidosis, LCDD deposits do not have affinity for Congo red stain. Immunofluorescence of the bone marrow usually demonstrates a monoclonal population of plasma cells</td>
</tr>
<tr>
<td>Heavy Chain Disease⁵</td>
<td>M protein with an incomplete heavy chain lacking a light chain</td>
</tr>
<tr>
<td>Systemic AL Amyloidosis⁶</td>
<td>Presence of an amyloid-related systemic syndrome, positive amyloid staining by Congo red or EM in any tissue, clear evidence that amyloid is light chain-related established by direct sub-typing of amyloid deposits, and evidence of a monoclonal plasma cell proliferative disorder</td>
</tr>
</tbody>
</table>
Diagnostic Criteria in Monoclonal Gammopathies

• MGUS
  – < 10% bone marrow plasma cells and M spike < 3 g/dl
  – Monoclonal protein / clonal plasma cell population
  – No End organ damage

• Myeloma
  – > 10% marrow plasma cells
  – End Organ Damage

• Indolent / Smoldering Myeloma
  – > 10% marrow plasma cells or M spike > 3 g/dl
  – No End organ damage
Criteria for End-Organ Damage in Monoclonal Gammopathies

• CRAB
  – Calcium > 1 mg/dl above ULN
  – Renal Insufficiency (> 2 mg/dl)
  – Anemia (< 10 g/dl)
  – Bone Lesions (lytic lesions or osteopenia)
A Model for Pathogenesis of Myeloma

Plasma cell events:
- Translocations at 14 q32 (50%)
- Deletion 13 (50%)
- Genomic instability

Microenvironment changes:
- ? infection
- ? inflammation

Normal → Microenvironment changes → MGUS → Angiogenesis → Myeloma

- N-Ras, K-Ras (30%)
- $P^{16}$ methylation (40%)
- ? secondary translocations

Bone resorption:
- ↑ RANKL, ↓ OPG, ↑ MIP-1α
- ↑ IL-6, ↑ VEGF
- ↓ immune surveillance
Multiple Myeloma Pathogenesis

- MM cells
- ICAM-1
- Bone marrow stromal cells
- Bone marrow vessels
- PBMC
- CD8+ T cells
- NK cells
- VEGF
- bFGF
- IL-6
- TNF-α
- IL-1β
- IL-2
- IFN-γ

Richardson, PG et al. Blood 2002
Monoclonal Gammopathy of Undetermined Significance (MGUS)

- Common, age-related
- Prevalence: 3.2% in persons over 50 yrs old (Minnesota)
  - ~5% in age >70

- Higher prevalence in African populations.
- ? Association with inflammatory states: obesity, Gaucher’s disease

- Increased risk for thrombosis and fractures

- Risk of progression in entire population: 1% /yr

- Risk factors for progression: %PC, level M spike, Free light chain, IgA protein, ?Decline in uninvolved Ig’s
Smoldering Myeloma (SMM)

- Patients with PC > 10% or M spike > 3 g/dl, but lacking CRAB symptoms.
- 10% per yr progression to overt MM
- Most eventually require therapy.
- Current recommendation is observation until progressive disease.
Disease Progression in MGUS and SMM

Risk Groups in Asymptomatic Myeloma

G1: BMPC >10% M > 3 g/dl;
G2: BMPC >10% M < 3 g/dl
G3: BMPC <10% M > 3 g/dl

Multiple myeloma

- Uncontrolled proliferation of Ig secreting plasma cells
  - most commonly IgG (57%), IgA (21%) or light chain only (18%)
- Twice as frequent in men as women, and in blacks as whites
- 1% of all cancers
  - 2% in African Americans
- Incurable
- Median survival 4-6 years
5 year survival (SEER)
Work-up in suspected myeloma

- Assessment of serum/urine protein
  - SPEP/IF, 24 hr urine for UPEP/IF
  - Free light chains (kappa, lambda)
- CBC, sCr, Calcium, Albumin, LDH,
- Serum beta 2 microglobulin (B2M)
- Skeletal survey
- Bone marrow aspirate and biopsy
  - Cytogenetics (including FISH)
- Under investigation:
  - MRI spine
  - PET scans
  - Bone densitometry, Urine n-telopeptide
Serum Free Light Chain (FLC)

- Quantitation of free $\kappa$ and $\lambda$ chains secreted by plasma cells\(^1\)
- An abnormal $\kappa/\lambda$ FLC ratio may be interpreted as a surrogate for clonal expansion\(^1\)
- FLC assay may be used for prognosis and disease monitoring\(^2\)
  - Abnormal FLC ratio is an important risk factor for disease progression\(^1\)
  - Useful in disease monitoring in the absence of measurable disease on SPEP and UPEP\(^3\)

* Kappa and Lambda FLC’s are both increased in renal failure/CKD
Key clinical aspects of myeloma

- Predominantly intra-medullary growth.
- Absence of clinical LN or spleen involvement.
- Low proliferative fraction.
- Long periods of stability in MGUS.
- Osteoclast activation, osteoblast inhibition, and bone loss.
- Multi-focal growth of tumor cells.
As many as 20% of patients with MM may be asymptomatic* at diagnosis²

- Increased BM PCs (≥10%)
- M Protein
- Anemia
- Lytic Bone Lesions
- Bone Pain
- Fatigue
- Weight Loss
- Renal Insufficiency
- Hypercalcemia
- Paresthesias

% Patients
Manifestations of Clonal Plasma Cell Proliferation

- ↑ Osteoclast
- ↓ Osteoblast
- LYTIC BONE DZ
- HYPERCALCEMIA

- ↓ Erythropoiesis
- ANEMIA

- ↑ Ig deposition
- Cast nephropathy
- RENAL FAILURE

- ↑ Immune-paresis
- Hypogamm
- INFECTION
At age 39, developed fatigue and bone pain from several fractures. She died 4 years later; autopsy showed that her marrow was replaced by a red, gelatinous substance.
Multiple Myeloma: Skeletal Complications
Romosozumab in Postmenopausal Women with Low Bone Mineral Density

Michael R. McClung, M.D., Andreas Grauer, M.D., Steven Boonen, M.D., Ph.D., Michael A. Bolognese, M.D., Jacques P. Brown, M.D., Adolfo Diez-Perez, M.D., Ph.D., Bente L. Langdahl, Ph.D., D.M.Sc., Jean-Yves Reginster, M.D., Ph.D., Jose R. Zanchetta, M.D., Scott M. Wasserman, M.D., Leonid Katz, M.D., Judy Maddox, D.O., Yu-Ching Yang, Ph.D., Cesar Libanati, M.D., and Henry G. Bone, M.D.
Figure 4. The Canonical Wnt–β-Catenin Signaling Pathway Used in Osteoblasts.
Renal Pathology in MM

Light Chain Deposition Disease

Light Chain Cast Nephropathy

AL Amyloid
Multiple Myeloma and Kidney Disease

- Often multifactorial cause: Uric Acid, Ca++, FLC
- Most strongly associated with increased filtered light chains
- Most commonly occurs around time of dx
- Conventional tests such as total protein, SPEP, urine dip stick don’t detect FLC
Metabolism and Excretion of Free Light Chains

- Glomerulus
- Cortex
- Outer medulla
- Inner medulla
- Light chains filtered
- 10 - 30g/day reabsorption
- Distal Tubule
- Proximal tubule
- Light chain deposition
- Collecting duct
- 5 - 10mg/day in urine

Adapted from Bradwell in Serum Free Light Chain Analysis (Fourth Edition)
International Staging System

• Stage I (B2M <3.5 mg/l; Albumin >3.5 g/dl)
  – Median OS 62 months

• Stage III (B2M >5.5 mg/l)
  – Median OS 29 months

• Stage II (Neither Stage I or III)
  – Median OS 44 months
Principles Of Treatment

• No evidence (yet) that early treatment prolongs survival
• Wait for symptoms, or evidence of disease progression, to start treatment
• Supportive measures are critically important
  – drink plenty of fluids daily
  – treat infections promptly
  – prophylactic bisphosphonates reduce skeletal complications in patients with osteopenia and lytic bone disease
  – anemia often responds to erythropoietin.
“Myeloma treatment is a marathon, not a sprint”
Management of Complications

- Anemia
  - Epo therapy*

- Infections
  - Vaccinations
  - IVIG

- DVT
  highest risk in imid+high dose dex or chemo
  no standard prophylaxis, ASA, Lovenox, Coumadin considered. Low
dose coumadin not very effective. Full anticoagulation recc. In high risk
pts.

(Leukemia 2008 vol 22)
Management of Complications

Bone Disease

Bisphosphonates - inhibit osteoclast mediated bone resorption
- Decrease risk of pathologic fracture
- Monthly x Two years then stop or q3 months if active dz
- Remember bisphosphonates may cause renal injury and nonselective proteinuria

- Radiotherapy (low doses achieve palliative benefit)
- Surgery
Normal

Multiple Myeloma

Pamidronate or Zoledronic Acid

Reduced risk of fracture in patients with lytic lesions
Management of Complications

- Renal Failure
  - Often Multifactorial
    - Nephrotoxic light chains
    - Hypercalcemia/volume depletion
    - Hyperuricemia

Treatment
- Fluid resuscitation
- Bisphosphonates
- Rasburicase/allopurinol
- Steroids
- Plasma Exchange?
- Treatment
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>1844</td>
<td>Rhubarb pill and orange peel infusion</td>
</tr>
<tr>
<td>1844</td>
<td>Phlebotomy and application of leeches as “maintenance”</td>
</tr>
<tr>
<td>1947</td>
<td>Urethane established as standard of care</td>
</tr>
<tr>
<td>1958</td>
<td>Melphalan</td>
</tr>
<tr>
<td>1962</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>1969</td>
<td>Melphalan + prednisone (MP) established</td>
</tr>
<tr>
<td>1974</td>
<td>Combination of carmustine + cyclophosphamide + melphalan + vincristine + prednisone</td>
</tr>
<tr>
<td>1983</td>
<td>Autologous stem cell transplant</td>
</tr>
<tr>
<td>1987</td>
<td>High-dose melphalan and stem cell rescue as standard therapy</td>
</tr>
<tr>
<td>1990</td>
<td>Introduction of novel agents</td>
</tr>
</tbody>
</table>
Major drugs in myeloma

- Alkylators - 1962
  - Melphalan, cyclophosphamide
  - High dose melphalan and ASCT

- Glucocorticoids - 1966
  - Prednisone, dexamethasone

- IMiDs - 1999
  - Thalidomide
  - Revlimid
  - Pomalidomide

- Proteasome Inhibitors - 2001
  - Bortezomib
  - Carfilzomib
Treatment course

Asymptomatic
- MGUS
- Stable MM

Symptomatic
- M protein
- Treatments

Acute
- Pancytopenia
- Plasma cell leukemia

Years
Months
Days
Cytogenetic Profiles of Myeloma

Carrasco et al Cancer Cell, Sawyer et al CGG, 2011
<table>
<thead>
<tr>
<th></th>
<th>Percentage of patients</th>
<th>Clinical and laboratory features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperdiploid</td>
<td>45</td>
<td>More favorable, IgG-κ, older patients.</td>
</tr>
<tr>
<td>Non-hyperdiploid</td>
<td>40</td>
<td>Aggressive, IgA-λ, younger individuals.</td>
</tr>
<tr>
<td>Cyclin D</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>translocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>16</td>
<td>Upregulation of CCND1; favorable prognosis; bone lesions. Two subtypes by GEP; CD20+ in one subset</td>
</tr>
<tr>
<td>t(6;14q)(p21;32)</td>
<td>2</td>
<td>Probably same as CCND1</td>
</tr>
<tr>
<td>t(12;14)(p13;q32)</td>
<td>&lt;1</td>
<td>Rare</td>
</tr>
<tr>
<td>MMSET</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>translocation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(4;14)(p16;q32)</td>
<td>15</td>
<td>Upregulation of MMSET; upregulation of FGFR3 in 75%; unfavorable prognosis with conventional therapy; bone lesions less frequent</td>
</tr>
<tr>
<td>MAF translocation</td>
<td>8</td>
<td>Aggressive</td>
</tr>
<tr>
<td>t(14;16)(q32;q23)</td>
<td>5</td>
<td>Confirmed as aggressive by at least two series</td>
</tr>
<tr>
<td>t(14;20)(q32;q11)</td>
<td>2</td>
<td>One series shows more aggressive disease.</td>
</tr>
<tr>
<td>t(8;14)(q24;q32)</td>
<td>1</td>
<td>Unknown effect on outcome but presumed aggressive.</td>
</tr>
<tr>
<td>Unclassified (other)</td>
<td>15</td>
<td>Various subtypes and some with overlap</td>
</tr>
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</table>
Factors Associated with Increased Disease Risk in MM

- Gene expression profile (GEP) 70 (or GEP15) high risk signature
- FISH:
  - t(4:14); t(14:16)
  - Del 17p
  - 1q amp; hypodiploidy
- Abnormal cytogenetics by metaphase, including del chr 13
- ISS Stage 3 (increased beta 2 m)
- High LDH
- > 10 focal lesions on MR
### TABLE 4. Risk Stratification of Active Multiple Myeloma

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FISH</strong></td>
<td>Del 17p</td>
<td>FISH t(4;14)</td>
<td>All others including:</td>
</tr>
<tr>
<td></td>
<td>t(14;16)</td>
<td>Cytogenetic del 13</td>
<td>FISH t(1;14)</td>
</tr>
<tr>
<td></td>
<td>t(14;20)</td>
<td>Hypodiploidy</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>PCLI ≥3%</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FISH = fluorescence in situ hybridization; GEP = gene expression profiling; PCLI = plasma cell labeling index.

### TABLE 5. Incidence and Median Overall Survival by Risk Group

<table>
<thead>
<tr>
<th>Factor</th>
<th>High risk</th>
<th>Intermediate risk</th>
<th>Standard risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence (%)</td>
<td>20</td>
<td>20</td>
<td>60</td>
</tr>
<tr>
<td>Median overall survival (y)</td>
<td>3</td>
<td>4-5</td>
<td>8-10</td>
</tr>
</tbody>
</table>
Initial therapy in myeloma

- Current approach based on risk status and potential candidacy for stem cell transplantation.
- Combination therapy superior to single agents.
Rationale for Combination Therapy in MM

IMiDs, Bortezomib → Mitochondria

Dex → Cytochrome-c, Smac

Bortezomib

Alkylators, Anthracyclines → NF-κB

Caspase-8 → Caspase-9 → Caspase-3 → PARP → Tumor cell death

Tumor cell death

Richardson PG et al, Expert Rev of AntiCancer Therapy 2008
High Response Rates to Induction Therapies in MM
High Risk

VRd

Intermediate Risk

VCD (CyBorD)

Standard Risk

Rd or CyBorD

Autologous stem cell transplantation, if eligible

Bortezomib based therapy for minimum of 1 yr

Not in VGPR: lenalidomide maintenance (2 yrs)

VGPR or better: no maintenance

Stem Cell Transplantation

- High-dose (marrow-ablative) therapy (HDT) with Autologous stem cell rescue
  - HDT Melphalan based
  - Sufficient liver, pulmonary, cardiac function necessary. Most data with pt age <65 years
  - Higher complete response rates, higher overall and event-free survival than with conventional chemotherapy (4-5 years)
IFM90 Trial of Conventional vs High-Dose Therapy With ASCT: OS

High dose therapy in myeloma

- Small randomized trials showing superiority to conventional therapy without ASCT (two with mature data).
- Early ASCT not superior to late ASCT.
- No conditioning regimen superior to melphalan alone.
- No benefit from CD34+ selected grafts.

- Superiority of SCT is being tested in the setting of new drugs.
Initial Therapy: Transplant *Ineligible*

- Melphalan + Prednisone was once the standard approach.

- RCTs show superiority of addition of thalidomide (MPT) or Velcade (MPV) to MP.

- Lenalidomide and dexamethasone is also active.
The future...

Antibody-dependent cellular cytotoxicity (ADCC)

Complement-dependent cytotoxicity (CDC)

Apoptosis/growth arrest via targeting signaling pathways

Effector cells

- ADCC

- FcR

- MM

- C1q

- CDC

- Daratumumab (CD38)

- huN901-DM1 (CD56)

- nBT062-maytansinoid (CD138)

- 1339 (IL-6)

- BHQ880 (DKK1)

- RAP-011 (activin A)

- Daratumumab (CD38)

- XmAb 5592 (HM1.24)

- Lucatumumab or dacetuzumab (CD40)

- Elotuzumab (CS1)

- Daratumumab (CD38)

JCO, 30(4), Feb 2012
Waldenström Macroglobulinemia

- Uncontrolled proliferation of lymphoplasmacytes producing IgM
- Median age 63 years
- Presents with weakness, fatigue, epistaxis, blurred vision
- Bone pain and lytic bone lesions are uncommon (<5%)
- 25% have hepatomegaly, splenomegaly and lymphadenopathy
- Hyperviscosity is common
TABLE 3. Diagnostic Criteria for Waldenström Macroglobulinemia and Associated Disorders

Waldenström macroglobulinemia

IgM monoclonal gammopathy (regardless of the size of the M protein) with >10% bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (surface IgM+, CD5−, CD10−, CD19+, CD20+, CD23−) that satisfactorily excludes other lymphoproliferative disorders, including chronic lymphocytic leukemia and mantle cell lymphoma.

IgM MGUS

Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytic infiltration <10%, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly.

Smoldering Waldenström macroglobulinemia (also referred to as indolent or asymptomatic Waldenström macroglobulinemia)

Serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥10% and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly, that can be attributed to a lymphoplasmacytic proliferative disorder.
Hyperviscosity syndrome

- bleeding (nasal and gums)
- blurred vision
- dizziness, headaches, ataxia
- congestive heart failure
- retinal vein engorgement, and papilledema
- rarely occurs with serum viscosity <4 centipoises (cp) (normal 1.8 cp)

![IgM pentamer]
Macroglobulinemia: Principles of Therapy

- Observation in patients with asymptomatic disease.

- Active drugs for therapy
  - Alkylating agents: Chlorambucil, Cytoxan
  - MAbs: Rituxan
  - Purine analogues: Fludarabine, Cladribine
  - Bendamustine
  - Steroids
  - Bortezomib
  - Thalidomide analogues
Plasma Cell Disorders Manifest Due to Clonal Immunoglobulin

AL Amyloid
Light chain deposition dz
Neuropathy
Cryoglobulinemia
Acquired vWD
Clinical Settings Where Ig Deposition Diseases (Including AL Amyloid) Should Be Suspected In Pts With Monoclonal Ig

- Congestive Heart Failure
- Neuropathy (including autonomic neuropathy)
- Nephrotic syndrome, Renal Failure
- Malabsorption
- Hepatosplenomegaly
- Carpal tunnel syndrome
- Macroglossia
- Unexplained constitutional symptoms
Diagnostic Approach in Suspected AL Amyloid

1. Clinical suspicion
2. Document amyloid deposit in tissues by Congo red staining or EM
3. Type the amyloid deposit
   - AL
   - AA
   - Hereditary amyloidosis
     - Exclude FAD
     - DNA analysis

   - AL
   - Other types, familial or reactive
Principles of Management in AL Amyloid

- Therapeutic approach guided by age, organ involvement.

- Cardiac involvement and dysfunction as a major predictor.

- Therapy directed at the underlying clonal plasma cells.
  - Melphalan
  - Steroids
  - Proteasome Inhibitors (Velcade)
  - Thalidomide/lenalidomide
Conclusion

• Plasma cell dyscrasias are a heterogeneous group of disorders.

• Clinical presentation may be due to the clone itself or the properties of the secreted Ig.

• Therapy largely directed (if indicated) at reducing the underlying clone.