Paraproteinaemias. Multiple myeloma. Amyloidosis.
Part 1

Dr. Gábor Mikala
Subtypes of Plasma Cell Disorders

• Increased Plasma Cells and Paraproteins
  – Monoclonal Gammopathy (of unknown significance, MGUS)
  – Multiple Myeloma (MM)
  – Waldenström’s Macroglobulinemia (WM, IgM)

• Increased / Altered Products of Plasma Cells (that may be few)
  – Light Chain Amyloidosis
  – Light Chain Deposition Disease
B cell Development As a Framework for Malignancies

Lymph node

Lymphoplasmacyte

Lymphoblast

Germinal Center

Plasmablast

Virgin B cell

Bone Marrow

Pre-B cell

Plasma cell

V(D)J RECOMBINATION

SOMATIC

HYPERMUTATION

SWITCH RECOMBINATION

G,A,E

IgM

IgM
B cell Development As a Framework for Malignancies

Lymph node

Germinal Center

SOMATIC HYPERMUTATION

Plasmablast

FOLLICULAR LYMPHOMA

Lymphoblast

BURKITT’S LYMPHOMA

Virgin B cell

CLL

WALDENSTROM’S

Lymphplasmacyte

IgM

MULTIPLE MYELOMA

G,A,E

Plasma cell

ALL

Pre-B cell

Bone Marrow
Epidemiology

New Cases of Cancer in the United States (2013 estimates)\(^1\)

- Non-Hodgkin lymphoma: 69,740
- Myeloma: 22,350
- Chronic lymphocytic leukemia: 15,000
- Acute myeloid leukemia: 14,590
- Hodgkin lymphoma: 9,290
- Other leukemia: 6,350
- Acute lymphocytic leukemia: 6,070
- Chronic myeloid leukemia: 5,920

Number of Cases (x1000)
Case Presentation

• 48 yo male
• Admitted with 2 wk history of fatigue and diffuse bone pain
• Evaluation:
  – Increased serum creatinine 500 umol/l
  – Increased serum calcium 2.9 mmol/l
  – Increased serum globulin 50 g/l (normal < 3 g/dl)
Evaluation of Abnormal Serum Globulins

Serum

Urine

Serum/Urine Protein Electrophoresis (S/UPEP)  Immunofixation Electrophoresis (IFE)

Serum M spike 40 g/l; typed as IgG kappa monoclonal Ig
Case Presentation…cont’d

Bone Marrow biopsy- Increased plasma cells
Skeletal survey—Lytic bone disease
Clinical spectrum of clonal expansions of transformed plasma cells in patients

- **MGUS**
  - Premalignant
  - Stable intramedullary expansion (benign?)
  - Asymptomatic.

- **Multiple myeloma**
  - Malignant
  - 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>
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<tbody>
<tr>
<td>Plasma Cell Leukemia&lt;sup&gt;1&lt;/sup&gt;</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 Plasmacytoma&lt;sup&gt;2&lt;/sup&gt;</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 Macroglobulinemia&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration</td>
</tr>
<tr>
<td>Light Chain Deposition Disease&lt;sup&gt;4&lt;/sup&gt;</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 Disease&lt;sup&gt;5&lt;/sup&gt;</td>
<td>M protein with an incomplete heavy chain lacking a light chain</td>
</tr>
<tr>
<td>Systemic AL Amyloidosis&lt;sup&gt;6&lt;/sup&gt;</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% clonal bone marrow plasma cells
  - End Organ Damage or very high risk thereof

- **Indolent / Smoldering Myeloma**
  - > 10% marrow plasma cells or M spike > 3 g/dl
  - No End organ damage and no high risk of that
Criteria for End-Organ Damage in Monoclonal Gammopathies

- **CRAB**
  - Calcium > 0.3 mmol/l above ULN
  - Renal Insufficiency (> 180 umol/l)
  - Anemia (< 100 g/l)
  - Bone Lesions (lytic lesions or osteopenia)

- **High risk of progression to symptomatic disease**
  - >60% marrow plasma cells
  - FLC ratio >100
  - >1 focal lesion on MRI
A Model for Pathogenesis of Myeloma

- Translocations at 14 q32 (50%)
- Deletion 13 (50%)
- Genomic instability
- N-Ras, K-Ras (30%)
- P16 methylation (40%)
- Secondary translocations

Microenvironment changes:
- Bone resorption (↑ RANKL, ↓ OPG, ↑ MIP-1α)
- IL-6, VEGF
- Immune surveillance
Multiple Myeloma Pathogenesis

- MM cells
- ICAM-1
- IL-6↑
- TNF-α↑
- IL-1β↑
- Bone marrow stromal cells
- VEGF
- bFGF
- Bone marrow vessels
- PBMC
- CD8+ T cells
- NK cells
- 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, neuropathy 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
  - Except in patients with extremely high risk of progression (defining events).
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 or low dose total body CT
- Bone marrow aspirate and/or biopsy
  - Cytogenetics (including FISH)
- Under investigation:
  - MRI spine
  - PET scans
  - Bone densitometry, Urine n-telopeptide
Serum Free Light Chain (FLC)

- Quantitation of free κ and λ chains secreted by plasma cells
- An abnormal κ/λ FLC ratio may be interpreted as a surrogate for clonal expansion
- FLC assay may be used for prognosis and disease monitoring
  - Abnormal FLC ratio is an important risk factor for disease progression
  - Useful in disease monitoring in the absence of measurable disease on SPEP and UPEP

* 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.
Clinical presentation

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
Historical aside...

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.

Figure 2. Sarah Newbury, the first reported patient with multiple myeloma. (A) Bone destruction in the sternum. (B) The patient with fractured femurs and right humerus. (C) Bone destruction involving the femur. Adapted from Solly° with permission.
Multiple Myeloma: Skeletal Complications
Bone Disease in MM

Myeloma cells

Tumor-derived osteoclast activating factors
- Macrophage inflammatory protein-1α (MIP-1α)
- IL-3

Tumor-derived osteoblast inhibitory factors
- DKK-1
- IL-3, IL-7

Stromal cell factors
- RANKL
- IL-6

Osteoclast

Osteoblasts

Bone

IL, Interleukin; DKK-1, Dickkopf homolog-1; RANKL, receptor-activated nuclear factor-kB ligand.
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

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

• Stage I (B2M <3.5 mg/l; Albumin >35 g/l)
  – 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 that early treatment prolongs survival – with the exception of extremely high risk of progression
• 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 rec. 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

Osteoclastic activity

Osteoblastic activity

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
# Myeloma Treatment: A Historical Perspective

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1844</td>
<td>Rhubarb pill and orange peel infusion</td>
</tr>
<tr>
<td></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>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, bendamustine
  - High dose melphalan and ASCT
- Glucocorticoids - 1966
  - Prednisolone, dexamethasone
- IMiDs – since 1999
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- Proteasome Inhibitors – since 2001
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Monoclonal antibodies – since 2016
  - Daratumumab, isatuximab
Treatment course

Asymptomatic
- MGUS
- Stable MM

Symptomatic
- M protein
- Treatments

Acute
- Pancytopenia
- Plasma cell leukemia
Cytogenetic Profiles of Myeloma

Carrasco et al Cancer Cell, Sawyer et al CGG, 2011
### IMWG Molecular Classification of Myeloma

<table>
<thead>
<tr>
<th>Percentage of patients</th>
<th>Clinical and laboratory features</th>
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<tbody>
<tr>
<td>Hyperdiploid</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>More favorable, IgG-κ, older patients.</td>
</tr>
<tr>
<td>Non-hyperdiploid</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td>Aggressive, IgA-λ, younger individuals</td>
</tr>
<tr>
<td>Cyclin D translocation</td>
<td>18</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>16</td>
</tr>
<tr>
<td></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>
</tr>
<tr>
<td></td>
<td>Probably same as CCND1</td>
</tr>
<tr>
<td>t(12;14)(p13;q32)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>MMSET translocation</td>
<td>15</td>
</tr>
<tr>
<td>t(4;14)(p16;q32)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Upregulation of MMSET; upregulation of FGFR3 in 75% unfavorable prognosis with conventional therapy; bone lesions less frequent, responds well to bortezomib</td>
</tr>
<tr>
<td>MAF translocation</td>
<td>8</td>
</tr>
<tr>
<td>t(14;16)(q32;q23)</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Confirmed as aggressive by at least two series</td>
</tr>
<tr>
<td>t(14;20)(q32;q11)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>One series shows more aggressive disease.</td>
</tr>
<tr>
<td>t(8;14)(q24;q32)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Unknown effect on outcome but presumed aggressive.</td>
</tr>
<tr>
<td>Unclassified (other)</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Various subtypes and some with overlap</td>
</tr>
</tbody>
</table>

IMWG. Leukemia 2010
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
- Any abnormal cytogenetics by metaphase, including del chr 13
- ISS Stage 3 (increased beta 2 microglobuline)
- High LDH
- > 10 focal lesions on MR
Initial therapy in myeloma

- Current approach based on risk status and potential candidacy for stem cell transplantation.

- Combination therapy superior to single agents: standard is triple combination (steroid + 2 active drugs)
Rationale for Combination Therapy in MM

IMiDs, Bortezomib → Mitochondria

Dex → Cytochrome-c

Bortezomib → Smac

Alkylators Anthracyclines → NF-κB

NF-κB → Caspase 9

Caspase 9 → Caspase 3

Caspase 3 → PARP

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
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

Overall Survival (%)

Month

Conventional dose
63 (53–73)
35 (22–50)
12 (1–40)

High dose
69 (58–78)
61 (50–71)
52 (36–67)

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 – benefit probably stays
Initial Therapy: Transplant *Ineligible*

- Melphalan + Prednisone was once the standard approach.

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

- Lenalidomide and dexamethasone is also active (probably superior to MPT, if maintained)
The future…

Antibody-dependent cellular cytotoxicity (ADCC)

Effector cells

Complement-dependent cytotoxicity (CDC)

Apoptosis/growth arrest via targeting signaling pathways

- Lucatumumab or dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb 5592 (HM1.24)

- Daratumumab (CD38)

- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

JCO, 30(4), Feb 2012