MGUS and MULTIPLE MYELOMA

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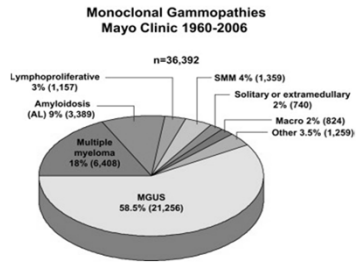
OBJECTIVES

- To explain the incidence, risk factors and spectrum of monoclonal gammopathies
- To explain the clinical scenarios in which to suspect multiple myeloma
- Explain the diagnostic methods for myeloma
- To discuss the latest diagnostic criteria and staging system for myeloma
- Talk briefly about the management of myeloma

MULTIPLE MYELOMA

- Multiple myeloma is a clonal plasma cell malignancy characterized by infiltration of bone marrow and end organ damage with or without the secretion of monoclonal protein in the serum and/or urine.
- Second most common hematological malignancy comprising 10% of all such diagnoses.
- Two thirds of patients are older than 65 years at diagnosis.

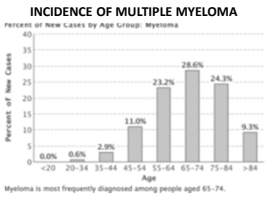
Prevalence of monoclonal gammopathies at Mayo clinic

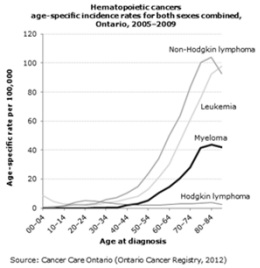


Risk factors for monoclonal gammopathies

- Race: Higher risk (twice) in African Americans compared to Caucasians
- Chemical and radiation exposure
  - Increased risk among those with pesticide exposure.
- Familial risk
  - Increased risk among first degree relatives

Incidence of myeloma

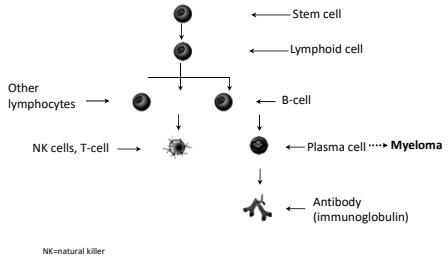




New cases 2016: 30,330
% of all cancers: 1.8%
5-year survival 2006-2012: 48.5%

https://seer.cancer.gov/statfacts/html/mulmy.html

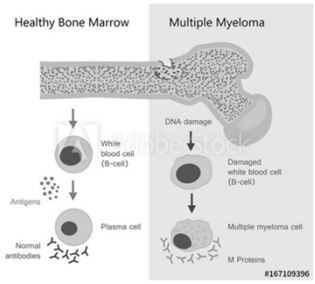
Normal Plasma Cell Development



Risk factors for monoclonal gammopathies

- Older age
- Immunosuppression
- Genetic predisposition
- Environmental exposures
- Secondary cytogenetic and marrow related changes

Pathogenesis of multiple myeloma



Multistep Pathogenesis of Multiple Myeloma

Multistep progressive	Intramedullary multiple myeloma	Intramedullary multiple myeloma	Extramedullary multiple myeloma	Plasma-cell leukemia
	Hyperdiploidy (50% of patients)			
Cytogenetic abnormalities		Secondary translocations		
	Non-hyperdiploidy (50% of patients)			
	Increased expression of cyclin D1, D2, and D3			
Other moledcular alterations		Oncogenic activation or mutation (RAS, FGFR3)		
			MYC dysregulation, TP53 mutation	

Palumbo A, Anderson K. N Engl J Med 2011;364:1046-1060.

Bone marrow microenvironment

Bone resorption

Angiogenesis

Key facts about myeloma

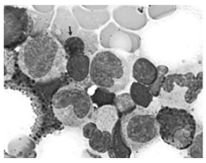
1. Diagnosis most often ages 65-70
2. Men 2:1
3. African-Americans ~ 2:1
4. Worst quality of life of any cancer
5. Survival has improved over last 10 years
6. But still virtually incurable for most patients
7. Universally evolves from “pre-malignant” state

Approach to Gammopathy

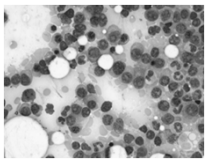
- Is it monoclonal? → No → Rheumatologic or hepatic diseases
- ↓
- Is there adenopathy? → Yes → Non-Hodgkin’s lymphoma?
- ↓
- Calcium, kidneys, and Hemoglobin normal? → Yes → MGUS or SMM
- ↓
- Are there CRAB criteria? → **Yes** → Myeloma ???

Precursor conditions
- **MGUS**
- **"Smoldering" myeloma**

CRAB CRITERIA
Calcium → High calcium
Renal → Renal (kidney) failure
Anemia → Reduced red blood cells
Bone → Bone fractures

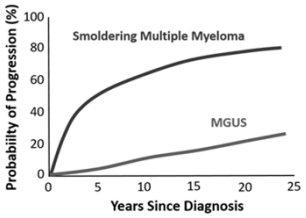


"normal marrow"



Marrow with multiple myeloma

Progression to symptomatic myeloma

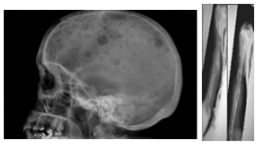


Risk Factors:
1. Type of M protein
2. Higher M spike
3. Higher plasma cell burden
4. Abnormal FLC ratio

Kyle et al. N Engl J Med 2007; 356:2582-2590

DIAGNOSIS OF MYELOMA

- Clonal bone marrow PC >/= 10%
- Serum and/or urine monoclonal protein
- End organ damage or CRAB features
  - Hypercalcemia
  - Renal failure
  - Anemia
  - Bone disease



When to suspect myeloma

- High serum protein with low albumin
- Unexplained hypercalcemia or renal failure
- pathological fractures
- Bone pain, unusual in nature
- Anemia, unexplained by other medical conditions

Examples of lytic bone disease

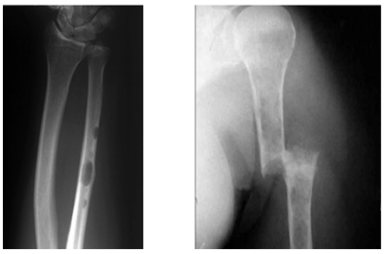


Table 1. Newly Added Criteria To Diagnose MM	
Clonal bone marrow plasma cells ≥10% or plasmacytoma plus one of these:	
	2-y Incidence of Organ Damage, %
Clonal marrow plasma cells ≥60%	95
Serum free light chain ratio ≥100	80[a]
≥ 2 focal bone lesions >5 mm on MRI	70-80
[a] 27% had acute renal failure as the myeloma-defining event. **MM**, multiple myeloma; **MRI**, magnetic resonance imaging	

Source: myelomacrowd.org

UPDATED IMWG CRITERIA FOR MM

MGUS	SMOLDERING MYELOMA	MULTIPLE MYELOMA
• M protein<3 g/dL and • BM clonal plasma cells<10% and • No myeloma defining events	• M protein>/=3 g/dL(serum) or >/= 500 mg/24 hr(Urine) or • BM clonal plasma cells>10% to 60% and • No myeloma defining events	• Underlying plasma cell proliferation • And 1 or more myeloma defining events • At least 1 CRAB feature • BM clonal PC>/=60% • At least one focal bone lesion on MRI • SFLC ratio>/=100

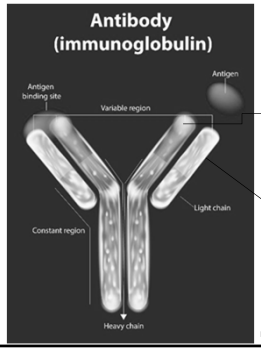
C: Serum calcium >11 mg/dL or >1 mg/dL than ULN
R: Serum creatinine >2 mg/dL or crcl<40 ml/min
A: Hemoglobin< 10 g/dL or >2 g lower than their baseline
B: >1 lytic bone lesion >/= 5 mm in size

OSU initial diagnostic studies

- Laboratory studies
  - CBC, electrolytes, kidney function, calcium, liver function tests
  - B_2Microglobulin, Albumin for ISS assessment
  - M-protein assessment – SPEP/IFE, UPEP/IFE, serum immunoglobulins, serum free light chains
- Bone marrow biopsy, Myeloma FISH panel
- Skeletal survey
- Consider baseline MRI T-spine, L-spine, pelvis without contrast (gadolinium)
- Consider PET

Detection of monoclonal protein

- Serum protein electrophoresis [SPEP] is a screening procedure to detect and quantify monoclonal protein.
- Serum immunofixation [IFE] is essential to label the heavy and light chains of the monoclonal protein [IgG, IgA, IgM; kappa and lambda].
- IFE helps differentiate monoclonal from polyclonal immunoglobulin and has more sensitivity compared with SPEP.



Can be IgG, IgA or IgM

Target of serum free light chain assay; kappa or lambda

Serum free light chains

- About one fifth of patients with myeloma produce only free light chains in the serum(Bence Jones proteins), and can be missed by routine immunofixation.
- SFLC assay is an antibody based system that can be used to diagnose light chain myeloma, systemic AL amyloidosis, light chain deposition disease

- NORMAL
- Serum free kappa LC: 3.3 to 19.4 mg/L
- Serum free Lambda LC: 5.7 to 26.3 mg/L
- Serum FLC ratio: 0.26 to 1.65
- Can be elevated in advanced renal failure
- Ratio >3 is less likely to be from renal failure alone

Uses of serum FLC assay

- Detection of light chain myeloma, systemic AL amyloidosis, LCDD
- Predicting the risk of progression of MGUS, SMM and solitary plasmacytoma to MM
- Documenting stringent complete response after achieving CR
- Can replace 24 hr UPEP at initial diagnosis when performed with SPEP/IFE

International Staging System (ISS)

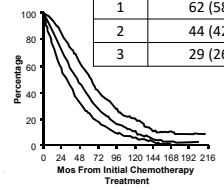
Better Response to Therapy	**Stage I** **Factors: beta-2 microglobulin <3.5 mg/dL** **Albumin ≥3.5 g/dL**	Most Favorable Prognosis
	Stage II **Factors: beta-2 microglobulin <3.5 mg/dL** **Albumin <3.5 g/dL or** **beta-2 microglobulin ≥3.5 – ≤ 5.5 mg/dL**	
Lesser Response to Therapy	**Stage III** **Factors: beta-2 microglobulin** **≥ 5.5 mg/dL**	Less Favorable Prognosis

Greipp et al. J Clin Oncol 2005; 23: 3412-20

International Staging System for *Symptomatic* Myeloma

Stage	Criteria
Stage I	$ß_2$-M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
Stage II	Not stage I or III
Stage III	$ß_2$-M ≥ 5.5 mg/L

ISS	Overall survival
1	62 (58-65)
2	44 (42-45)
3	29 (26-32)



Greipp PR, et al. J Clin Oncol. 2005;23:3412-3420.

Risk stratification of myeloma

Risk group	Percentage of newly diagnosed patients with the abnormality
Standard Risk	75%
Trisomies	
t(11;14)	
t(6;14)	
Intermediate Risk	10%
t(4;14)	
Gain(1q)	
t(11;14)	
High Risk	15%
t(14:16)	
t(14;20)	
del(17p)	

Revised ISS

- Goal was to incorporate FISH and cytogenetic abnormalities to make the staging system comprehensive and better predicitive of prognosis.
- Presence of del(17p), t(4;14), or t(14;16) were considered high risk.

R-ISS	ISS	iFISH	LDH	OS
1	β2M < 3.5, Alb ≥ 3.5	Standard	Normal	**NR**
2				**83 mos.**
3	β2M ≥ 5.5	High risk or high		**43 mos.**

Palumbo A et al. Revised International Staging System for Multiple Myeloma: A report from the international myeloma working group. *JCO* 33, 3-Aug-2015.

Overall survival (OS) in patients with MM stratified by revised International Staging System (R-ISS)

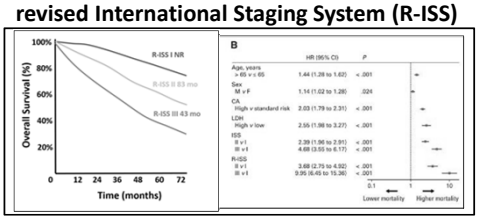


Fig 1. (A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm. Median OS was not reached for patients included in R-ISS stage I, whereas it was 83 months for R-ISS stage II and 43 months for R-ISS stage III. (B) Univariable analysis of OS. CA, chromosomal abnormalities; F, female; HR, hazard ratio; LDH, lactate dehydrogenase; M, male; NR, not reached.

Palumbo et al, JCO 33: 2863-2869

Published in: Antonio Palumbo, Hervé Avet-Loiseau, Stefania Oliva, Henk M. Lokhorst, Hartmut Goldschmidt, Laura Rosiñol, Paul Richardson, Simona Caltagirone, Juan José Lahuerta, Thierry Facon, Sara Bringhen, Francesca Gay, Michel Attal, Roberto Passera, Andrew Spencer, Massimo Offidani, Shaji Kumar, Pellegrino Musto, Sagar Lonial, Maria T. Petrucci, Robert Z. Orlowski, Elena Zamagni, Gareth Morgan, Meletios A. Dimopoulos, Brian G.M. Durie, Kenneth C. Anderson, Pieter Sonneveld, Jesus San Miguel, Michele Cavo, S. Vincent Rajkumar, Philippe Moreau; *Journal of Clinical Oncology* **2015**, 33, 2863-2869.
DOI: 10.1200/JCO.2015.61.2267

Response criteria in myeloma

	PR	VGPR	nCR	CR	sCR
Serum Protein electrophoresis	**> 50%**	**>90%**	**0**	**0**	**0**
Urine Protein electrophoresis	**>90%**	**< 100 mg/24 hrs**	**0**	**0**	**0**
Serum/Urine Immunofixation			**Positive**	**Negative**	**Negative**
Bone marrow PC			**<5%**	**<5%**	**<5%**
Bone marrow immunoflorescence					**Negative**
Serum Free light chain ratio					**Normal**

Source: Duri et al, Leukemia. 2006 Sep;20(9):1467-73

Immunomodulators

- IMiDs bind to cereblon and inhibits cereblon E3 ligase activity, resulting in cell cycle arrest through impaired DNA repair, replication and transcription .
- May cause direct cytotoxicity by inducing free radical mediated damage
- Also have antiangiogenic and TNF alpha inhibitory properties

Proteasome inhibitors

- Proteasomes are multienzyme complexes that help maintain protein homeostasis through clearance of misfolded/unfolded and cytotoxic proteins
- Bortezomib, being a proteasome inhibitor, inhibits proliferation and induces apoptosis in MM cells resistant to conventional therapies
- In combination with dexamethasone, it overcomes resistance to apoptosis conferred by IL-6 or adhesion to bone marrow stromal cells

Pharmacology in myeloma

DRUG	CLASS	ROUTE	SIDE EFFECTS
Bortezomib (Velcade)	PI	SC	*PN, *VZV reactivation, cardiac, cytopenias, diarrhea, local pain
Carfilzomib (Kyprolis)	PI	IV	*Cardiovascular, pulmonary, renal, GI, cytopenias
Ixazomib (Ninlaro)	PI	Oral	PN, VZV reactivation, edema, cytopenias, diarrhea, *eye disease
Thalidomide	IMId	Oral	CNS, *PN, DVT/PE, skin
Lenalidomide (Revlimid) Pomalidomide (Pomalyst)	IMId	Oral	*Thrombocytopenia, *DVT/PE, skin, GI
Panobinostat (Farydak)	HDACi	Oral	Cardiac, diarrhea

Choice of induction regimen

- Three drug regimen standard for patients who are fit and eligible for auto SCT
- The triplet should include a PI and Dexamethasone, as PI have activity in high risk disease

Patient related	Disease related	Non-medical
1. Age 2. Performance 3. Comorbidities: Peripheral neuropathy DM, CHF 4. Resources	1. Prognostic features – risk 2. Disease presentation 3. Organ impairment due to disease	1. Patient preferences 2. Financial resources 3. Availability of drug

Induction regimen

- VRd is the standard induction regimen for both transplant eligible and ineligible patients with NDMM.
- If Lenalidomide is not available for use as initial therapy or in the presence of ARF, other Bortezomib containing regimens such as VTd or VCd can be used instead of VRd.
- Rd is recommended for patients who are unable to tolerate a triplet regimen due to advanced age, comorbidities or poor PS.

Standard treatment for "fit" patients

1. Treatment until end organ damage reverses and good disease response is obtained (usually 3-4 months)

Drug	Type	Mode	Side Effects
Dexamethasone	Steroid	Pill weekly	insomnia, weight gain
Lenalidomide	IMiDs (immune modulating)	Pill daily	blood clots, diarrhea
Bortezomib	Proteasome Inhibitors	Shot 2x / wk subcutaneous	tingling numbness in hands or feet

2. Autologous stem cell transplant = High dose IV melphalan
6 weeks of drug prep prior to transplant; 16 day hospital stay
(Leads to 30 months of remission on average)

3. Lenalidomide (pill) maintenance
(Adds 18 months of remission on average)

Standard treatment for "unfit" patients

1. Treatment until damaged organs are as good as they are going to get (usually 3-4 months)

Drug	Type	Mode	Side Effects
Dexamethasone	Steroid	Pill weekly	insomnia, weight gain
Lenalidomide	IMiDs (immune modulating)	Pill daily	blood clots, diarrhea
Bortezomib	Proteasome Inhibitors	Shot 2x / wk subcutaneous	tingling numbness in hands or feet

2. Lenalidomide (pill) or bortezomib (SQ) maintenance

Neuropathy - bortezomib

- Can occur abruptly and can be painful, debilitating.
- Greatly diminished by weekly once and subcutaneous administration, without losing efficacy.
- Duloxetine, effective in other chemo induced neuropathy, can be used in BIPN.

Bone disease

- Bone disease is an important cause of morbidity in MM
- Treatment and prevention of skeletal lesions is a vital part of management of MM
- Bone disease is mediated by IL-6 and osteoclast activating factor (OAF)
- Bisphosphonates are an integral part of treatment of MM

Bone disease

- Bisphosphonates inhibit bone resorption by suppressing osteoclast activity
- Also affect the microenvironment in which tumor cells grow and may have direct anti-tumor activity
- Prevent skeletal events, reduce bone pain, and ?potentially prolong survival(Zoledronic acid)
- Risk for bisphosphonate-related osteonecrosis of jaw (BRONJ)
- Denosumab – moab to RANKL – approved for patients with renal failure

RELAPSED/REFRACTORY DISEASE

Management

- Second gen PI – Carfilzomib
- Immunomodulators – Pomalidomide
- Monoclonal antibodies – Daratumumab(CD 38)
- Histone deacetylase inhibitor – Panabinostat
- Metabolism inhibitors
- Chimeric Antigen Receptor –T cell therapy

Oncological emergencies in myeloma

- Hypercalcemia:
- Can be asymptomatic or present with nausea, vomiting, polyuria, polydipsia, constipation, abdominal pain, altered mentation or seizures
- iv fluids, bisphosphonates [do not wait for dental clearance]
- Calcitonin for rapid reduction
- Hemodialysis for extremely high levels

Oncological emergencies in myeloma

- Cord compression
- Suspect in patients with back pain, motor/sensory deficits, bowel/bladder dysfunction
- Can be due to extramedullary plasmacytoma or bone fragments from fractures
- Prompt administration of steroids immediately followed by imaging
- Radiation and/or surgery as needed

Oncological emergencies in myeloma

- Febrile neutropenia
- Often a complication from chemotherapy
- Prompt initiation of broad-spectrum antibiotics after initial work up for infection [chest x ray, blood and urine cultures]
- Aggressive fluid resuscitation
- Vasopressor and ventilator support as needed