



MGUS and Multiple Myeloma

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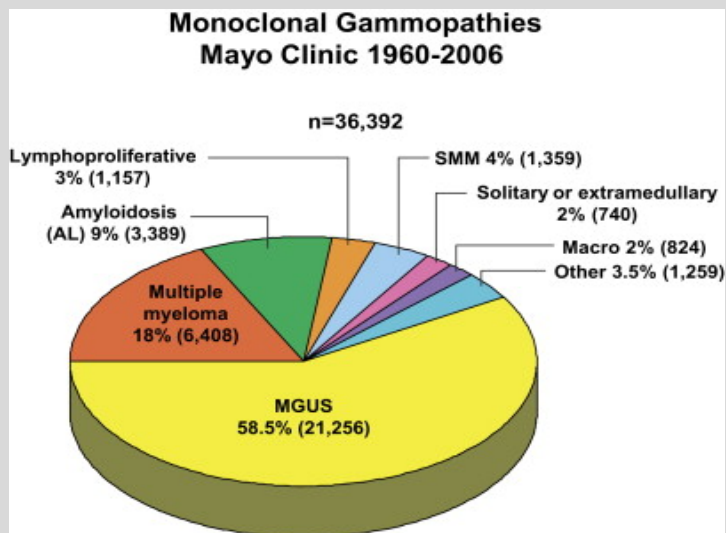
OBJECTIVES

- 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

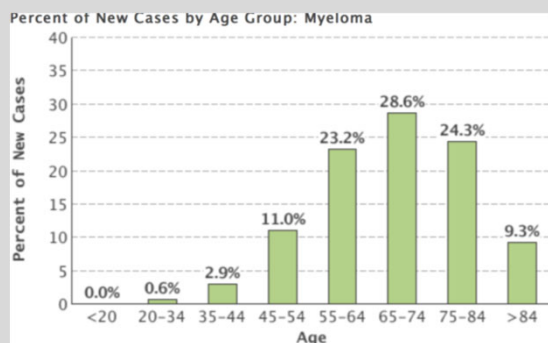


Risk factors for monoclonal gammopathies

- 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

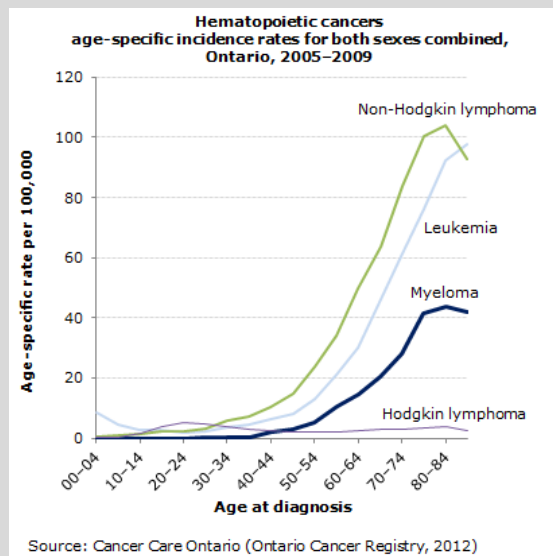
INCIDENCE OF MULTIPLE MYELOMA



New cases 2016: 30,330

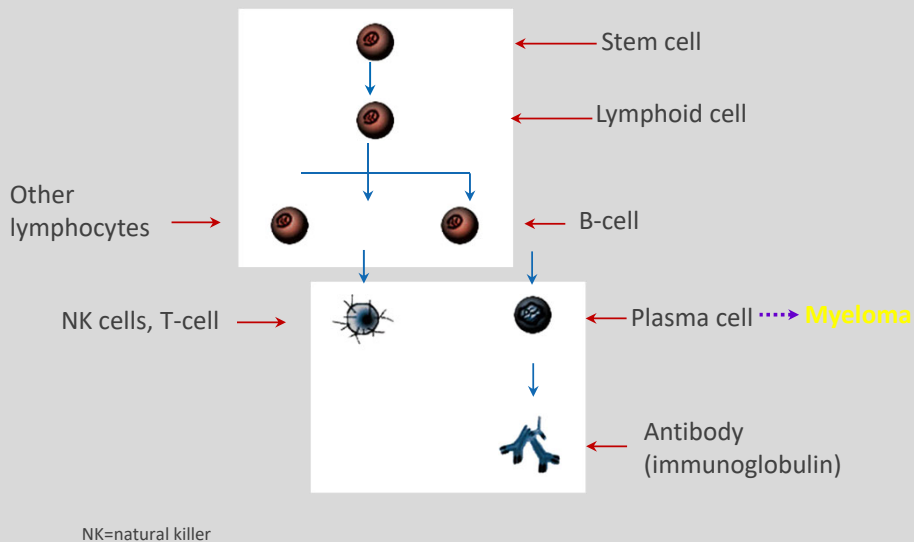
% of all cancers: 1.8%

5-year survival 2006-2012: 48.5%



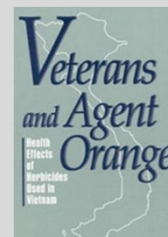
<https://seer.cancer.gov/statfacts/html/mulmy.html>

Normal Plasma Cell Development

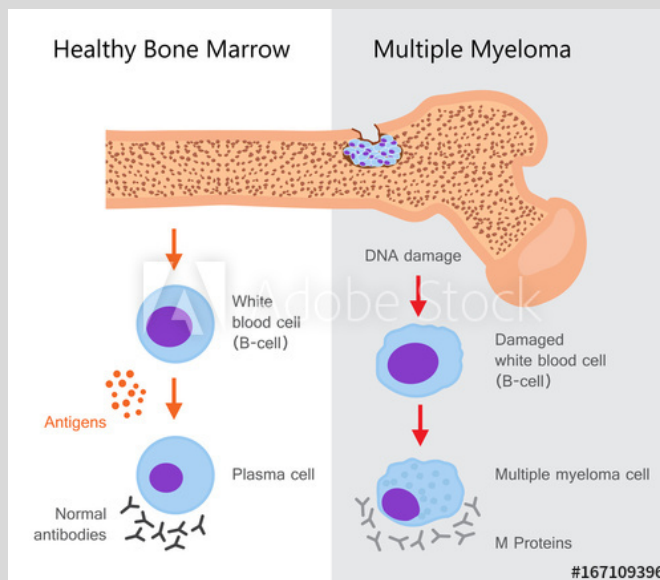


Risk factors for monoclonal gammopathies

- 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 molecular 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

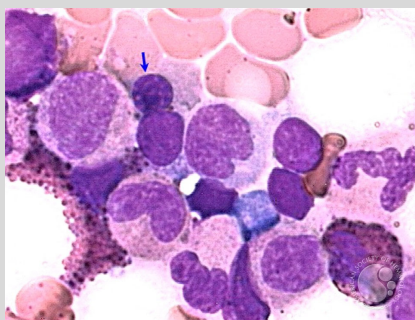
- Is it monoclonal? No → Rheumatologic or hepatic diseases
- ↓
- Is there adenopathy? Yes → Non-Hodgkin's lymphoma?
- ↓
- Calcium, kidneys, and Hemoglobin normal? Yes → MGUS or SMM
- ↓
- Are there CRAB criteria? Yes → Myeloma ???

Precursor conditions

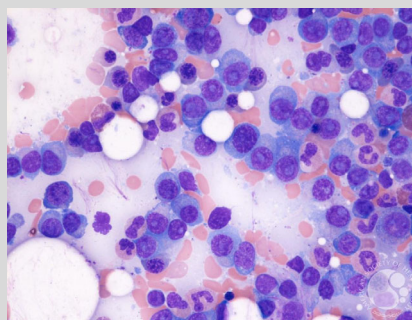
- MGUS
- "Smoldering" myeloma

CRAB CRITERIA

- C**alcium → High calcium
- R**enal → Renal (kidney) failure
- A**nemia → Reduced red blood cells
- B**one → Bone fractures

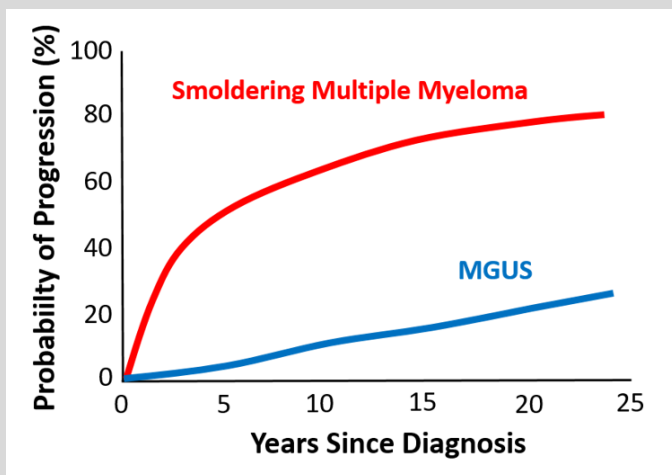


"normal marrow"



Marrow with multiple myeloma

Progression to symptomatic myeloma



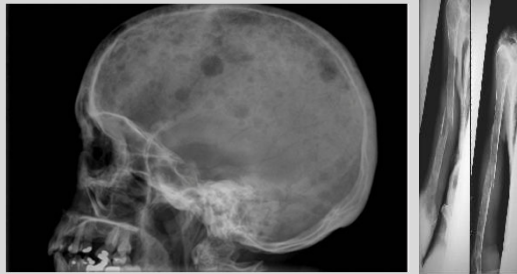
Risk Factors:

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 \geq 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

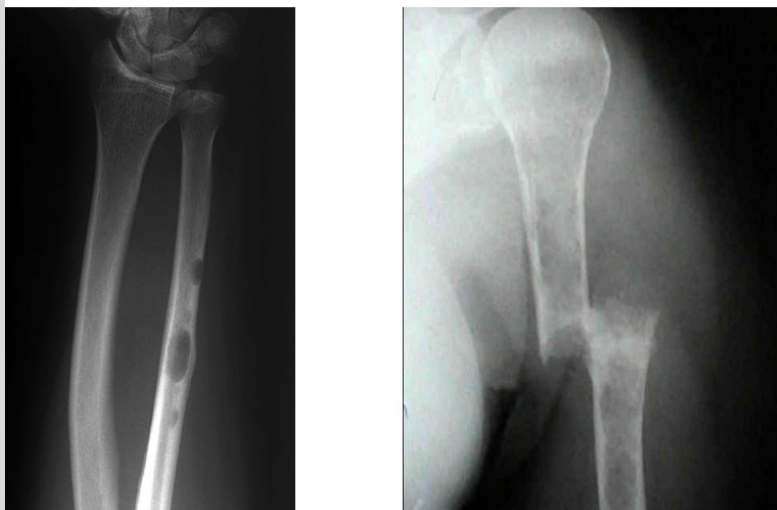


Table 1. Newly Added Criteria To Diagnose MM

Clonal bone marrow plasma cells $\geq 10\%$ or plasmacytoma plus one of these:

	2-y Incidence of Organ Damage, %
Clonal marrow plasma cells $\geq 60\%$	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
<ul style="list-style-type: none"> M protein < 3 g/dL <p>and</p> <ul style="list-style-type: none"> BM clonal plasma cells < 10% <p>and</p> <ul style="list-style-type: none"> No myeloma defining events 	<ul style="list-style-type: none"> M protein \geq 3 g/dL (serum) or \geq 500 mg/24 hr (Urine) or BM clonal plasma cells > 10% to 60% <p>and</p> <ul style="list-style-type: none"> No myeloma defining events 	<ul style="list-style-type: none"> Underlying plasma cell proliferation And 1 or more myeloma defining events At least 1 CRAB feature BM clonal PC \geq 60% At least one focal bone lesion on MRI SFLC ratio \geq 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

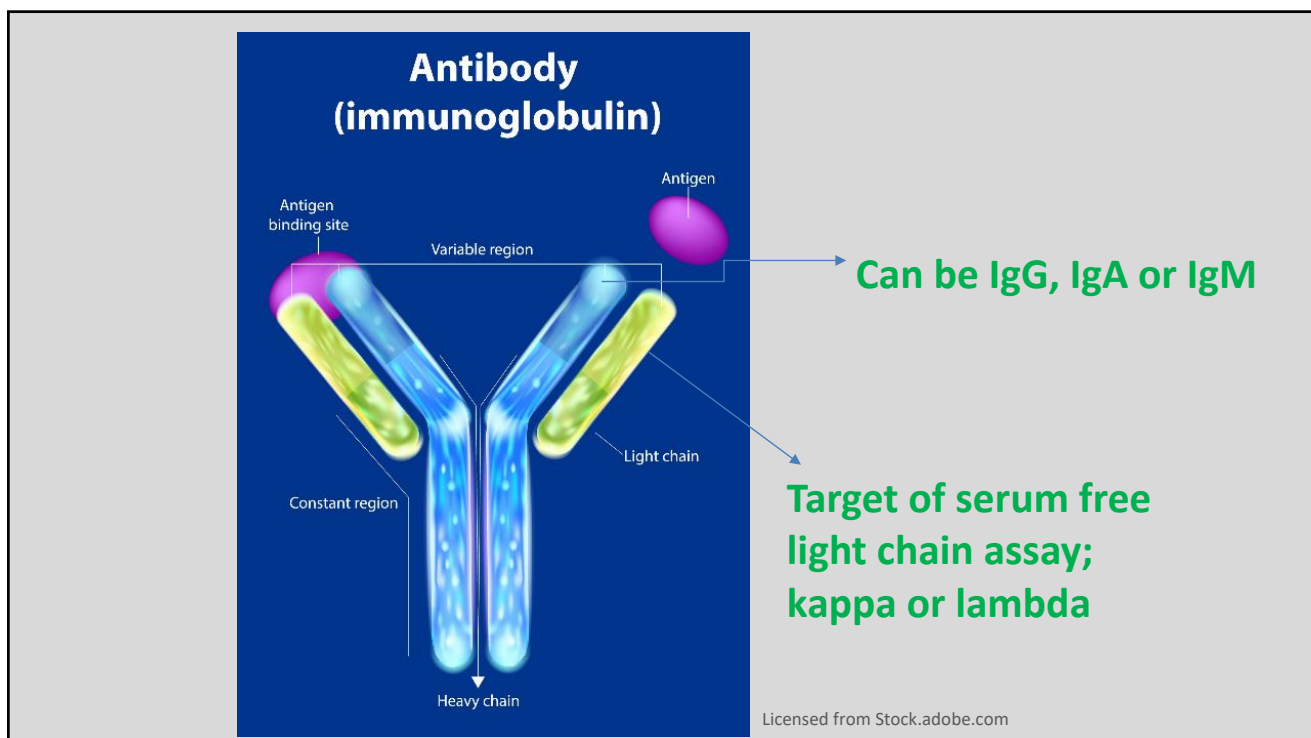
B: > 1 lytic bone lesion \geq 5 mm in size

OSU initial diagnostic studies

- Laboratory studies
 - CBC, electrolytes, kidney function, calcium, liver function tests
 - B₂ Microglobulin, 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.



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.
- SFCL 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

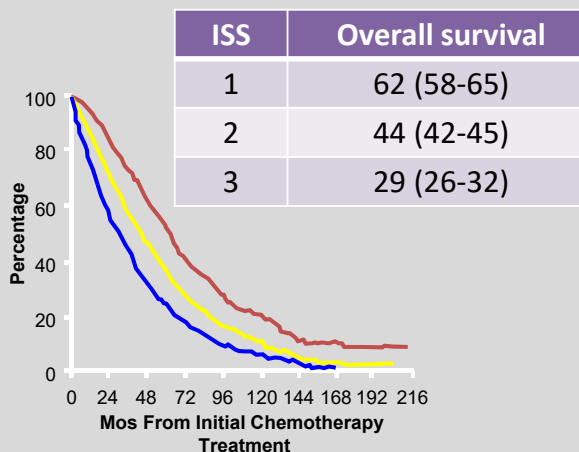
International Staging System (ISS)

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	β_2 -M < 3.5 mg/L and serum albumin ≥ 3.5 g/dL
Stage II	Not stage I or III
Stage III	β_2 -M ≥ 5.5 mg/L



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 predictive of prognosis.
- Presence of del(17p), t(4;14), or t(14;16) were considered high risk.

R-ISS	ISS	iFISH	LDH	OS
1	$\beta 2M < 3.5$, Alb ≥ 3.5	Standard	Normal	NR
2				83 mos.
3	$\beta 2M \geq 5.5$	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)

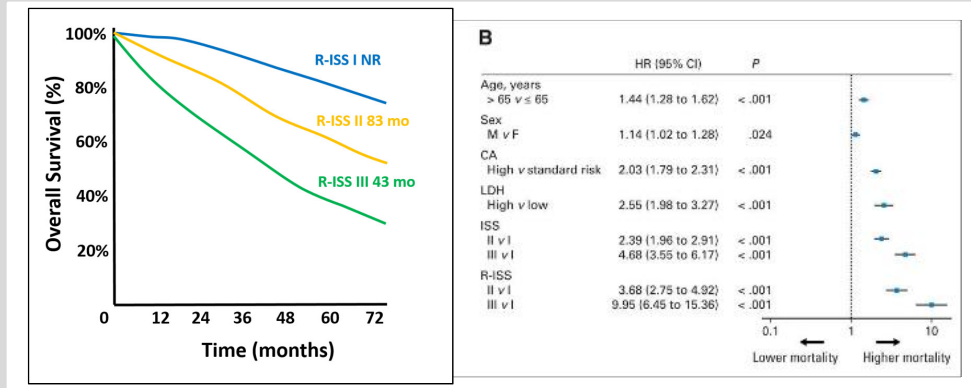


Fig 1. (A) Overall survival (OS) in patients with multiple myeloma stratified by revised International Staging System (R-ISS) algorithm. Median OS was not reached for patients included in R-ISS stage I, whereas it was 83 months for R-ISS stage II and 43 months for R-ISS stage III. (B) Univariable analysis 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 Rosinol; Paul Richardson; Simona Caltagirone; Juan José Lahuerta; Thierry Facon; Sara Brinchen; 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; Jesús San Miguel; Michele Cavo; S. Vincent Rajkumar; Philippe Moreau, *Journal of Clinical Oncology* 2015, 33, 2863-2869.
 DOI: 10.1200/JCO.2015.61.2267
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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 immunofluorescence					
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

1. Age
2. Performance
3. Comorbidities:
Peripheral neuropathy
DM, CHF
4. Resources

Disease related

1. Prognostic features – risk
2. Disease presentation
3. Organ impairment due to disease

Non-medical

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 – Panabinstat
- 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