Myeloma
Update on Treatment and Side Effects Management

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Welcome & Introductions

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Myeloma Update on Treatment and Side Effects Management

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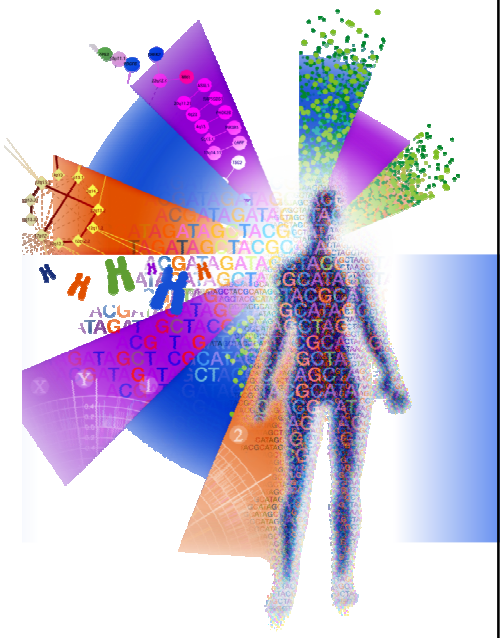
Professor of Medicine
Chair, Hematology & Oncology



Clinical Presentation

- Incurable
- Cancer of plasma cells
- Marrow plasmacytosis
- Osteolytic bone lesions
- Renal dysfunction or failure
- Aberrant immunoglobulin production
- Aberrant protein deposition – amyloid
- Immune compromised state - infections

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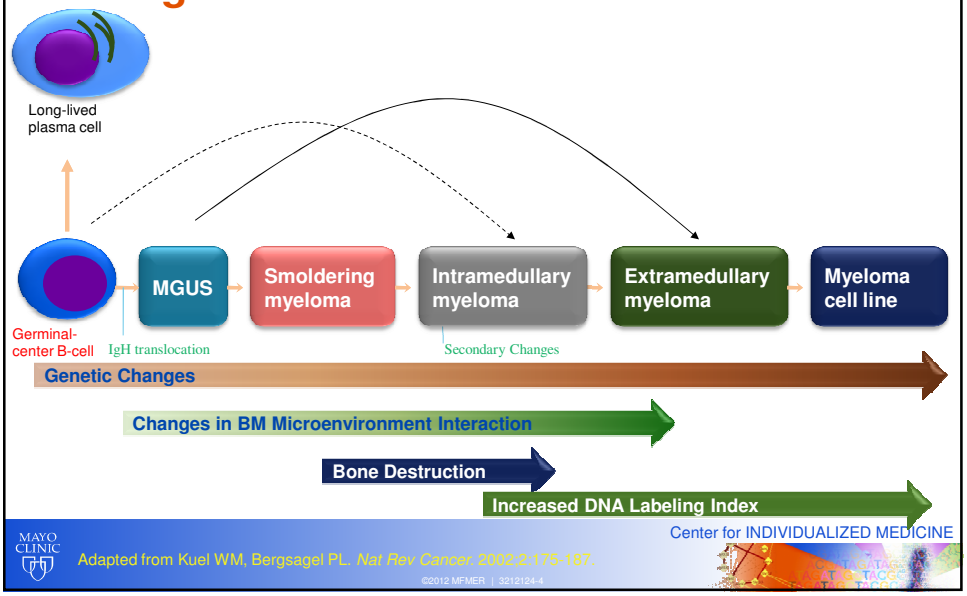
Pathogenesis



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Adapted from Kuel WM, Bergsagel PL. *Nat Rev Cancer.* 2002;2:175-187.

Center for INDIVIDUALIZED MEDICINE

Diagnosis & Staging
Initial Diagnostic Evaluation

- History and physical examination
- Blood workup
  - CBC with differential and platelet counts
  - BUN, creatinine
  - Electrolytes, calcium, albumin, LDH
  - Serum quantitative immunoglobulins
  - Serum protein electrophoresis and immunofixation
  - β_2-microglobulin
  - Serum free light chain assay
- Urine
  - 24-hr protein
  - Protein electrophoresis
  - Immunofixation electrophoresis
- Other
  - Skeletal survey
  - Unilateral bone marrow aspirate and biopsy evaluation with immunohistochemistry or flow cytometry, cytogenetics, and FISH
  - MRI as indicated

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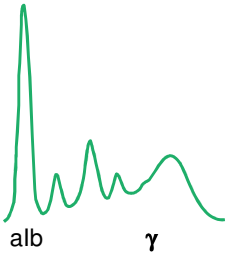
NCCN. Practice guidelines: myeloma. V.3.2010. Available at: http://www.nccn.org.

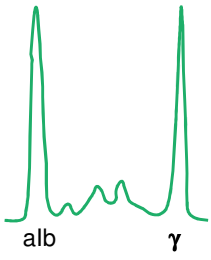
Diagnosis & Staging
Serum Protein Electrophoresis

Normal

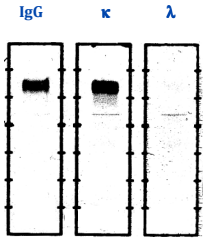


Gamma region:
Small broad peak

Monoclonal Protein in Myeloma



Gamma region:
Sharp peak



Abnormal serum immunofixation: 93%

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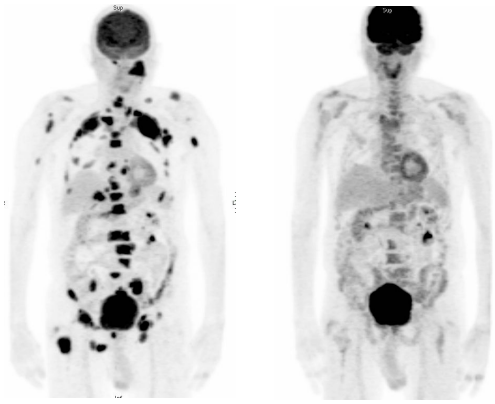
Kyle RA, et al. Cecil textbook of medicine, 22nd edition. Elsevier; 2004. Image courtesy Steven Fruitsmaak. Available at: http://commons.wikimedia.org/wiki/File:Monoclonal_gammopathy_Multiple_Myeloma.png.

PET-Scan to Identify Focal Lesions



Sher et al. Leuk & Lymp. 2010

Criteria for Diagnosis of Myeloma

MGUS	Smoldering MM	Active MM
< 3 g M spike	≥ 3 g M spike	≥ 10% PC
< 10% PC	OR: ≥ 10% PC	M spike +
AND		AND
No anemia, no bone lesions; normal calcium and kidney function		Anemia, bone lesions, high calcium, or abnormal kidney function

Kyle RA, et al. N Engl J Med. 2002;346:564-569.

TREATMENT APPROACH

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Introduction

- Last decade exceptionally promising for Myeloma.
- Several new drugs have been approved
- This had a direct survival advantage to patients.
- Improved biological stratification can prevent unnecessary aggressive treatments to all patients.
- Long-term planning is critical
- Selection of appropriate (first or subsequent) therapy is important.

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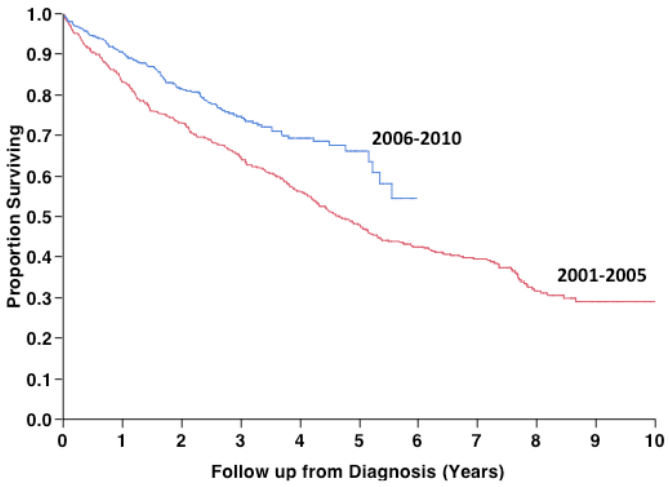
Improving survival over time



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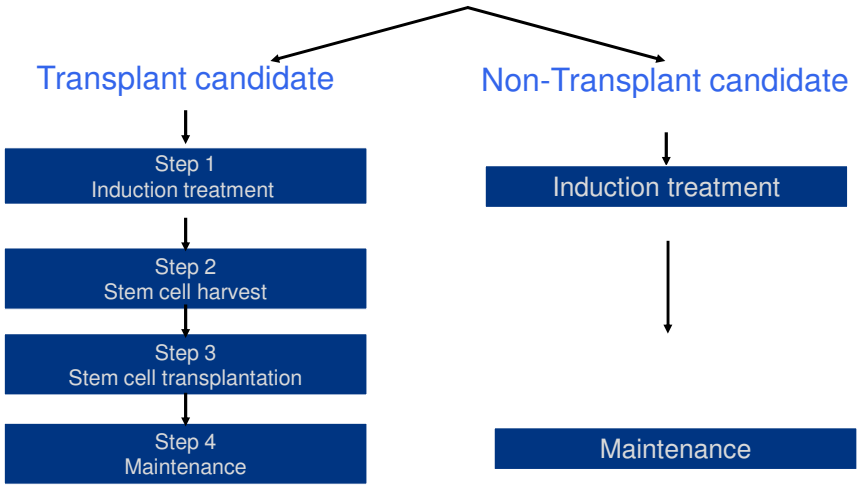
Kumar et al: ASH 2012, Publication 3972

Initial Approach to Treatment of MM



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Risk Stratification of Active MM

High	Intermediate	Standard
FISH	FISH	All others including
Del 17p	t(4;14)	hyperdiploidy
t(4;14)		t(11;14)
t(14;20)	del 13 (cytogen)	t(6;14)
	hypodiploidy	
GEP		
High risk	PCLI ≥3%	

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Incidence and Median OS by Risk Group

	High Risk	Intermediate Risk	Standard Risk
Incidence	20%	20%	60%
Median Overall Survival	3 years	4-5 years	8-10 years

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Mikhael et al 2013

Anti-Myeloma Therapeutics

Class	Drug Available
Alkylating agents	Melphalan Cyclophosphamide Bendamustine
Anthracyclines	Doxorubicin Liposomal doxorubicin
Corticosteroids	Dexamethasone Prednisone
Immunomodulatory drugs	Thalidomide Lenalidomide Pomalidomide
Proteasome inhibitors	Bortezomib Carfilzomib
Others	Arsenic trioxide/Vit. C Zoledronic Acid Pamidronate

Therapeutic "Tools" to Treat Myeloma

- Steroids
- Melphalan (Transplant)
- Alkylating Agents
- IMiDs
- Proteasome Inhibitors
- Anthracyclines
- Bisphosphonates

→

Combination Regimens
Vdex
Vdox
RD
TD
MP

VCD
VRD
VdoxT
VTD
VMP
MPT
MPR

CLINICAL TRIALS

Selection of Best Therapeutic Options Based on Patient Risk Category

STANDARD RISK

- 60% of the Cases
- Median Survival 8-10 years
- Sequential therapy approach
- Choice of Induction therapies
  - Len / Dex (response rate 80%)
  - Bort / Dex (response rate 80%)
  - Bort / Thal / Dex (response rate 93%)
  - Cyt / Bor / Dex
  - Carfil / Cyt / thal / Dex (response rate 96%)
- Duration of induction treatment (4-6 cycles)

Mikhael et al 2013

HIGH RISK

- 20% of the Cases
- Median Survival 3 years
- Aggressive and continuous treatment
- Choice of Induction therapies
  - Bort / Len / Dex
  - Bort / Thal / Dex
  - Bort / Cyt / Dex
  - Duration of induction treatment (4-6 cycles)

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NEW APPROVED DRUGS

Pomalidomide

Carfilzomib

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Phase 1 trials				
	Patient population	N	Regimen/dose	ORR
Schey	Relapsed	24	Pom dose escalation MTD 2mg 28/28	54%
Streetly	Relapsed	20	Pom +/- dex MTD 5 mg QOD 28/28	50%
Richardson	Rel/refr	38	Pom +/- dex MTD 4 mg 21/28	25%
Phase 2 trials				
Richardson	Len/Btz ref	120	Pom +/- dex, 4 mg, 21/28	25%
Lacy	Rel, 1-3 reg	60	Pom/dex 2 mg, 28/28	63%
Lacy	Len ref	34	Pom/dex 2 mg, 28/28	47%
Leleu	Len/Btz ref	43 40	Pom/dex 4 mg, 21/28 Pom/dex 4 mg, 28/28	30% 47%
Lacy	Len/Btz ref	35 35	Pom/dex 2 mg, 28/28 Pom/dex 4 mg, 28/28	49% 43%
Mark	RR/MM	52	Cla/ Pom +/- dex, 4 mg, 21/28	60%

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Responses

	2mg Relapsed ≤ 3 Reg	2mg Len Refractory	2mg Bortz/Len Refractory	4mg Bortz/Len Refractory	4mg Relapsed ≤ 3 Reg	4mg Relapsed D 1-21
All cycle Confirmed Response Rate	65%	32%	26%	29%	38%	23%
No. of Responders	39	11	9	10	23	28
Median time to response	1.7 mo	2.0 mo	1mo	1.4mo	1.1mo	1.1mo

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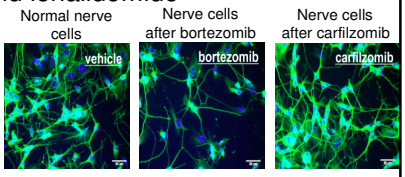
Patient Outcomes

	2mg Relapsed ≤ 3 Reg	2mg Len Refractory	2mg Bortz/Len Refractory	4mg Bortz/Len Refractory	4mg Relapsed ≤ 3 Reg	4mg Relapsed D 1-21
Median Duration of response[1]	21 mo	8 mo	15 mo	3 mo	22 mo	10 mo
Median Overall Survival[1]	NA	33mo	16mo	14 mo	NA	14mo
9 Month OS	91%	81%	68%	54%	83%	66%
Median Progression Free Survival[1]	13 mo	5 mo	6 mo	3 mo	8 mo	4 mo

Mo: month; NA: Not attained
1) Kaplan Meier Estimate, median (95% confidence interval)

Carfilzomib

- Approved for the treatment of relapsed/refractory myeloma
- Effective in patients who are bortezomib and lenalidomide resistant disease (20% ORR)
- Low incidence of peripheral neuropathy



Response	Overall (n=257)	Patients with poor high-risk disease
Median months on treatment	3 (0.03 – 16.9)	3.6 (0 – 11.1)
Overall response (≥PR)	61 (24%)	21 (29.6%)
Clinical benefit rate*	95 (37%)	24 (33.8%)
VGPR	13 (5%)	3 (4.2%)
Median duration of response (months)	7.8 (5.6 – 9.2)	7 (3.7 – 8.5)

Arastu-Kapur et al Clin Cancer Res May 1, 2011 vol. 17 no. 9 2734-2743
Siegel et al Blood. 2012 Oct 4;120(14):2817-25.

PROMISING NEW AGENTS

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Drug (Company)	Class	Development stage
elotuzumab (AbbVie/Bristol-Myers Squibb)	Anti-CS1 moAb	phase 3
ixazomib (MLN9708, Millennium Pharmaceuticals)	Oral proteasome inhibitor	phase 3
melphalan intravenous (Ligand Pharmaceuticals/Spectrum Pharmaceuticals)	Alkylating agent	phase 3
panobinostat (LBH589, Novartis)	HDAC inhibitor	phase 3
plitidepsin (Aplidin, PharmaMar)	Cyclodepsipeptide (Oxidative stress activator)	phase 3
tabalumab (Eli Lilly)	Anti-BAFF moAB	phase 3
vorinostat (Zolinza, Merck)	HDAC inhibitor	phase 3
ACY-1215 (Acetylon Pharmaceuticals)	HDAC6 inhibitor	phase 2
ALT-801 (Altor BioScience)	Mutant p53-specific scTCR/IL-2 fusion protein	phase 2
ARRY-520 (Array BioPharma)	kinesin spindle protein (KSP) inhibitor	phase 2
AT7519 (Astex Pharmaceuticals)	Cyclin-dependent kinase (CDK) inhibitor	phase 2
AT9283 (Astex Pharmaceuticals)	Pan-Aurora Kinase inhibitor	phase 2
AUY922 (Novartis)	HSP-90 inhibitor	phase 2
BHQ880 (Morphosys, Novartis)	DKK1 neutralizing antibody	phase 2
BIW-8962 (BioWa/Kyowa Hakko Kirin)	Anti-ganglioside GM2 moAB	phase 2
BT-062 (Biotest Pharmaceuticals/ImmunoGen)	CD138-antibody-maytansinoid conjugate	phase 2
daratumumab (Janssen Biotech)	Anti-CD38 moAB	phase 2
darinaparsin (ZIO-101, Ziopharm Oncology)	Arsenic cytotoxin	phase 2
delanzomib (Cephalon [Teva])	Oral proteasome inhibitor	phase 2
GL-0817 (Gliknik)	MAGE-A3 multipeptide vaccine	phase 2
GVAX Multiple Myeloma (BioSante Pharmaceuticals)	Myeloma vaccine	phase 2
imetelstat (Geron)	Telomerase inhibitor	phase 2
KW-2478 (Kyowa Hakko Kirin)	HSP-90 inhibitor	phase 2
mapatumumab (HGS-ETR1, GlaxoSmithKline)	TRAIL-R1 activating moAb	phase 2
milatuzumab-doxorubicin conjugate (Immunomedics)	Anti-CD74-moAb-doxorubicin conjugate	phase 2
palbociclib (PD-0332991, Pfizer)	CDK 4/6 inhibitor	phase 2
PRLX-93936 (Prolexsys Pharmaceuticals)	Novel RAS pathway inhibitor	phase 2
PVX-410 (OncoPep)	Multipeptide myeloma vaccine	phase 2
siltuximab (CNTO-328, Janssen Biotech)	Anti-IL6 moAb	phase 2
TH-302 (EMD Serono/Threshold Pharmaceuticals)	Hypoxia-activated DNA alkylating agent	phase 2
TKI258 (Novartis)	Multitargeted receptor tyrosine kinase (RTK) inhibitor	phase 2

31 therapeutic agents currently in phase 2/3 development for MM.

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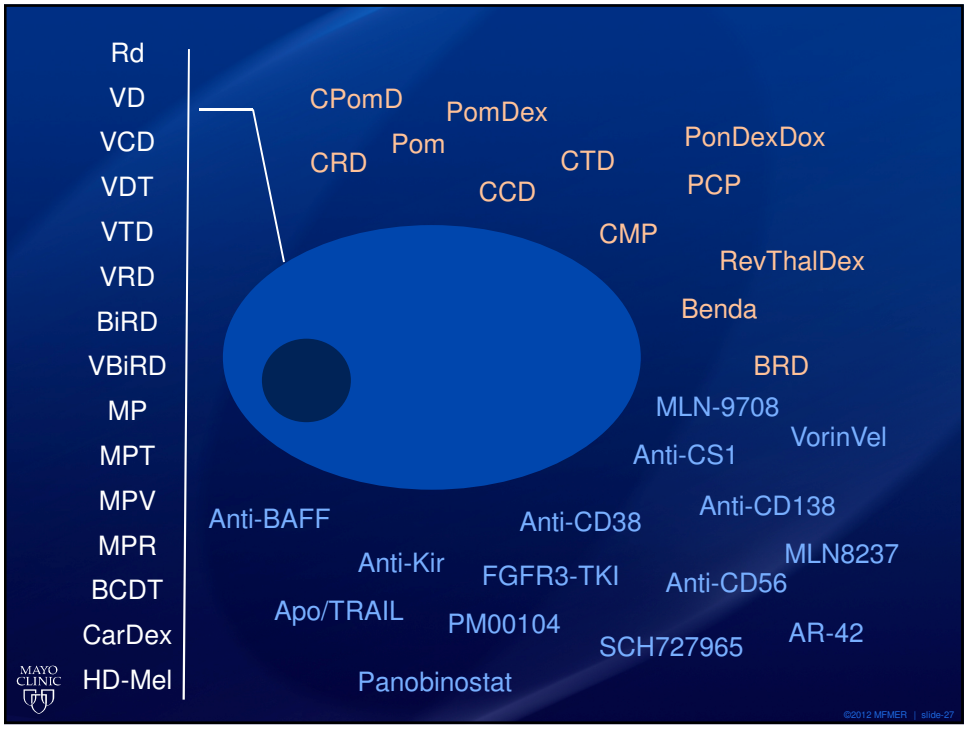

Select Phase 2/3 Clinical Trials in Myeloma

Treatment	Mechanism of action	Stage of development
Ixazomib	Reversible Proteasome inhibitor	Phase 3
Elotuzumab	CS1 monoclonal antibody	Phase 3
Panobinostat	HDAC inhibitor	Phase 3

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Clinicaltrials.gov 2013

Select Phase 2/3 Clinical Trials in Myeloma

Treatment	Mechanism of action	Stage of development
Tabalumab	Anti-BAFF antibody	Phase 2/3
Daratumumab	CD38 monoclonal antibody	Phase 2
IPH2101	Anti-KIR antibody	Phase 2
CT-011 + MM/DC fusions	Immunotherapy / Vaccination	Phase 2
Poly-ICLC + MAGE-A3 vaccine	Immunotherapy / Vaccination	Phase 2/3

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Clinicaltrials.gov 2013

A Phase 2 Study of Elotuzumab (Elo) in Combination with Lenalidomide and Low-Dose Dexamethasone in Relapsed/Refractory Multiple Myeloma: Updated Results

- Elotuzumab (Elo) is a humanized monoclonal IgG1 antibody targeting CS1, a cell surface glycoprotein highly expressed on >95% of MM cells
- 73 pts were treated (10 mg/kg, n=36; 20 mg/kg, n=37).
- ORR was 84%; 92% with 10 mg/kg and 76% for 20 mg/kg
- Median PFS in the 10 mg/kg cohort was 26.9 mos and in the 20 mg/kg cohort was 18.6 mos
- Most common Aes were lymphopenia (19%), neutropenia (18%), thrombocytopenia (16%), anemia (12%), leukopenia (10%), hyperglycemia (10%)

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Richardson et al, Sunday, December 9, 2012: 5:15 PM

SIDE EFFECT MANAGEMENT

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Anemia

- Monitor your own hemoglobin
  - Mild
  - Moderate
  - Severe
- Symptoms
  - Fatigue, breathlessness, palpitation, sleepiness
- Causes
  - Disease
  - Chemotherapy
  - Radiation therapy
  - Bone marrow transplant
- Management
  - Depends on severity and range from
    - No treatment and just monitoring
    - Blood transfusion(s)
    - Erythropoietin injections
    - Holding treatment and restarting
    - Reducing treatment dose

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Thrombocytopenia – Low Platelets

- Can monitor your own levels
  - Mild
  - Moderate
  - Severe
- Symptoms
  - Red spots on skin, nose or gum bleeding
- Causes
  - Disease (rare)
  - Chemotherapy
  - Velcade
- Management
  - Depends on severity and range from
    - No treatment and just monitoring
    - Platelet transfusion(s)
    - Holding treatment
    - Reducing treatment dose

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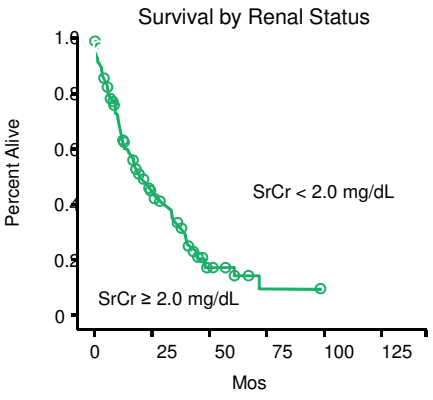
Renal Failure Adversely Affects Survival in Patients With MM

- Renal failure at diagnosis associated with increased mortality
- Median OS
  - 40.3 mos in patients with baseline SrCr ≥ 2.0 mg/dL
  - 19.5 mos in patients with SrCr < 2.0 mg/dL



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Eleutherakis-Papaiakovou V, et al. Leuk Lymphoma. 2007;48:337-341.

Kidney Damage

- Monitor Serum Creatinine
- Symptoms
  - none
- Causes
  - Disease
    - Cast nephropathy
    - Hypercalcemia
    - Hyperuricemia
    - Dehydration
    - Hyperviscosity
    - Amyloidosis or light chain deposition
  - Dye given with CT scans
- Management
  - Depends on severity and range from
    - Hydration
    - Use of bortezomib (Velcade ®) or drugs in the same class
    - Avoid CT scan dyes
    - Avoid pain killers such as ibuprofen or

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Herpes Zoster or Shingles with Bortezomib

Rationale for HZV Prophylaxis With Bortezomib Treatment

- Rationale supported by 2 analyses
- Phase III APEX trial of bortezomib vs dexamethasone[1]
  - Routine prophylaxis: 25% vs 46%
  - HZV infections: 13% vs 5% ($P = .002$)
  - Total infections: 24% vs 21% ($P = .443$)
- Retrospective analysis of 125 patients with MM treated with bortezomib (median: 16 wks) and HZV prophylaxis[2]
  - Acyclovir 400 mg QD in > 80% of patients; alternatives: acyclovir 200 mg, valacyclovir 250/500 mg, or famciclovir 500 mg QD
  - Self-reported adherence: 100%
  - No episodes of HZV infection

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1. Chanan-Khan AA, et al. J Clin Oncol. 2008;26:4784-4790.
2. Vickrey E, et al. Cancer. 2009; 115:229-232.

Neuropathy

- Sensory or Motor
  - Mild
  - Moderate
  - Severe
- Symptoms
  - Numbness, tingling, pain, burning sensation
- Causes
  - Disease itself
  - bortezomib (Velcade ®)
  - Thalidomide
- Management
  - Depends on the cause and the severity
    - No treatment and just monitoring
    - Disease treatment
    - Kyphoplasty
    - Neurontin / Lyrica
    - If drug related – hold Rx or adjust dose
    - Vitamin supplements

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Deep Vein Thrombosis (*Blood Clot*)

- Symptoms
  - Pain/swelling in Calf
  - Breathlessness even at rest
- Causes
  - Thalidomide
  - Revlimid
  - Pomalidomide
- Prevention with
  - Aspirin
  - Warfarin
  - Heparin
- Management
  - Treat with warfarin
  - or Heparin
  - Treatment can continued once adequate anticoagulation achieved.

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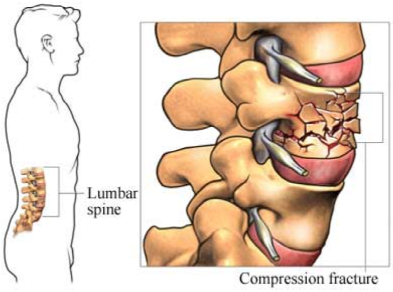
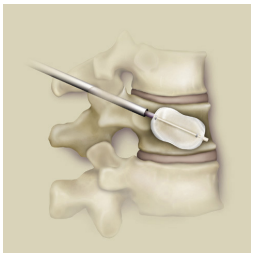
Vertebral Body Fracture





Advantages:

- Relieves pain[1,2]
- Restores 34% to 53% of vertebral height[1-3]
- Cement leakage occurs in ~4%[2]

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1. Fourney DR et al. *J Neurosurg Spine*. 2003;98:21-30. 2. Dudeney S et al. *J Clin Oncol*. 2002;20: 2382-2387. 3. Lane JM et al. *Clin Orthop*. 2004;426:49-53.

Bisphosphonates

- Reduced incidence of SREs and need for RT[1]
- Zoledronic acid as effective as pamidronate in reducing risk of skeletal-related events[2]
- Long-term treatment associated with osteonecrosis of the jaw[3]
  - Risk higher with zoledronic acid
- Dose- and infusion rate–related renal toxicity[4]

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1. Berenson JR, et al. Cancer. 2001;91:1191-1200; 2. Rosen LS, et al. Cancer J. 2001;7:377-387. 3. Dimopoulos MA, et al. Haematologica. 2005;91:968-971. 4. Berenson JR. Oncologist. 2005;10:52-62.

Osteonecrosis of the Jaw - ONJ

- 60% of the cases follow a dental procedure
- 50% occur in the mandible
- 70% occur posterior to the cuspids

Badros, et al. J Clin Oncol. 2006; 24(6):945-52.

Thank You for inviting me

Myeloma group at Mayo

Rochester

- V. Rajkumar, MD
- Francis Buadi, MD
- David Dingli, MD
- A Dispenzieri, MD
- Morie Gertz, MD
- Suzanne Hayman, MD
- Shaji Kumar, MD
- Robert Kyle, MD
- Nelson Leung, MD
- John Lust, MD
- Steve Russell, MD
- S Zeldenrust, MD
- Prashant Kapoor, MD
- Arleigh McCurdy, MD

Arizona

- Leif Bergsagel, MD
- Rafael Fonseca, MD
- Joseph Mikhael, MD
- Craig Reeder, MD
- Keith Stewart, MD

Florida

- Vivek Roy, MD
- Asher Chanan-Khan, MD
- Taimur Sher, MD
- Aneel Paulus, MD
- Kasyapa Chitta, PhD

Myeloma
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Question and Answer Session

Dr. Chanan-Khan's slides are available for download at
www.LLS.org/programs

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MYELOMA AND CAREGIVER ONLINE CHATS

- **Every Tuesday evening from 8:00 PM – 10:00 PM ET**
- **Visit www.LLS.org/chat to register or for more information**

The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified myeloma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE: www.LLS.org/copay**
- **TOLL-FREE PHONE: (877) LLS-COPAY**

For more information about myeloma and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL: infocenter@LLS.org**