APSHO Regional Lecture Series

Accredited Educational Activities for Advanced Practitioners in Oncology

Collaborative Practice in the Management of Patients With Cancer

Management of Newly Diagnosed Multiple Myeloma Patients

Program Chair

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APSHO Regional Lecture Series

Disclosures

Faculty

Ms. Kurtin has served as consultant for Amgen, BMS, Celgene, Genentech, Incyte, Janssen, Novartis, Takeda, and Pharmacyclics.

Planning Committee

Moshe C. Ornstein, MD, MA, Cleveland Clinic Taussig Cancer Institute (Reviewer) has nothing to disclose. Alana Brody, Terry Logan, Lynn Rubin, and Wendy Smith (MEI) have nothing to disclose. Sandy Leatherman, Annamarie Luccarelli, and Jessica Tamasi (APSHO) have nothing to disclose. Claudine Kiffer and Annie Yueh (Harborside Press) have nothing to disclose.

Learning Objectives

- Describe the various mechanisms of action of agents used to treat multiple myeloma (MM)
- Apply the principles of risk-adapted treatment using case-based scenarios to illustrate the impact of patient attributes and disease-specific attributes in MM
- Manage toxicities associated with newer agents used to treat MM
- Apply the principles of adjunctive supportive care in the treatment of patients with MM

MULTIPLE MYELOMA OVERVIEW

Multiple Myeloma Epidemiology

New Cases (US, 2015)	Deaths (US, 2015)	Mean Age at Diagnosis, Yrs	5-Yr Overall Survival 1975 – 2011 (p<0.5)
30,330	12,650	69	Increased by 23.8%

- Risk factors
  - Unknown in the majority of cases
  - Increased with age, male sex, obesity, and black race
- Survival
  - In 2012, there were an estimated 89,568 people living with MM (survivors) in the United States
  - 5-year OS has increased from 24.7% (1975-1977) to 48.5% (2005-2011) (p<.05)
- Variable response to treatment and variation in survival
  - From a few months to > 10 yr
  - High-risk attributes are thought to play a primary role
  - 20% of patients survive >10 yr, regardless of therapy
  - Novel agents may neutralize the effects of some high-risk features
  - Achievement of minimal residual disease negative (MRD-) status early in the course of disease is key

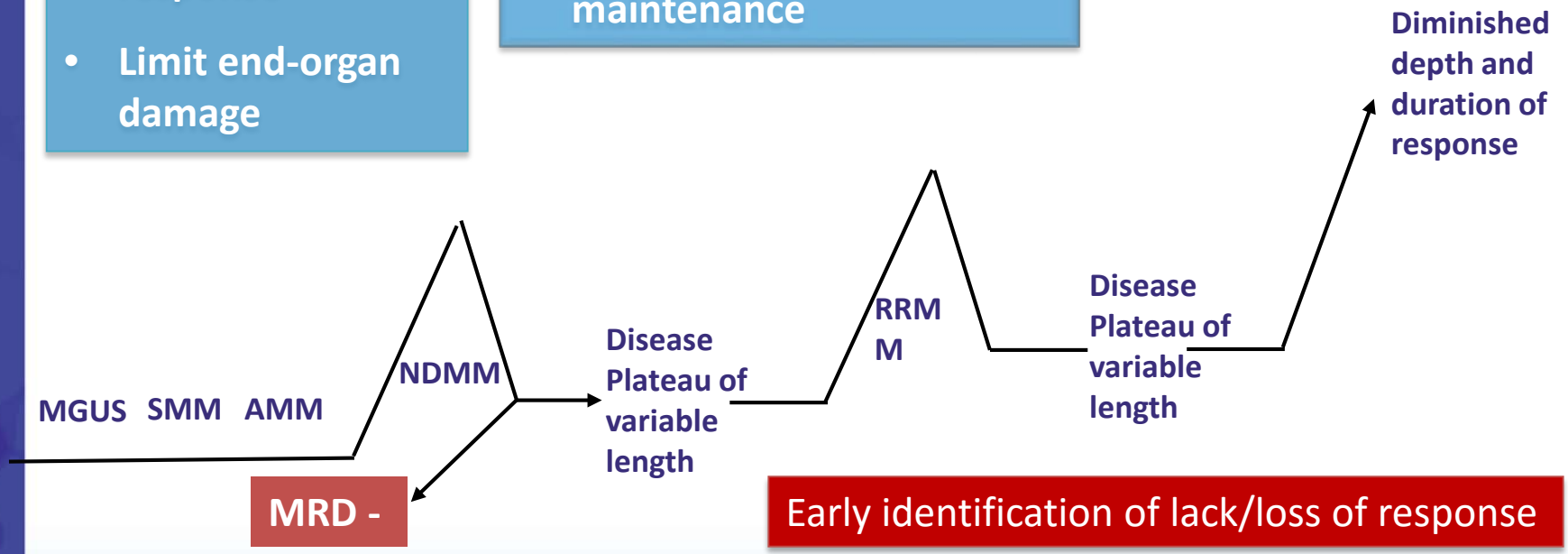
Badros. *J Natl Compr Canc Netw*. 2010;8(suppl 1):S28-S34; Siegel L, et al. (2016). Cancer statistics, 2016. *CA Cancer J Clin* 66(1), 7-30; Kumar SK, et al. Presented at ASH. 2012. Abstract 3972; Kumar SK, et al. *Blood*. 2008;111:2516-2520; http://seer.cancer.gov/statfacts/html/mulmy.html

Natural History of Multiple Myeloma

- Initiation of the best available treatment to induce an early and deep response
- Limit end-organ damage

- Optimizing each treatment option to achieve and maintain MRD- status
- Use of AHSCT consolidation and/or maintenance

Salvage therapy considering disease and personal factors



MM = multiple myeloma; MGUS = monoclonal gammopathy of uncertain significance; SMM =aAsymptomatic MM; NDMM = newly diagnosed MM; MRD0 = minimal residual disease negative; RRMM = relapsed and/or refractory MM

Rajkumar et al., 2014 et al., 2013; Ludwig et al., 2014; Mikael et al., 2013; NCCN, 2016; Palumbo et al., 2015; Palumbo et al., 2014; Adapted from Kurtin, S. 2016.

Common Presenting Signs and Symptoms

- Most common complaint at presentation is bone pain and fatigue
- Signs and symptoms result from an overproduction of immunoglobulins with secondary processes

Disease Process	Symptoms	Clinical Findings
Plasma cell invasion of the bone	• Bone pain (58%) • Hypercalcemia	• ***Lytic lesions (66%)**** • Compression fractures or other skeletal fractures • ***Hypercalcemia (13%)**** • Osteoporosis, osteopenia • Cord compression
Bone marrow involvement	• Fatigue (32%) • Infections • Bleeding	• ***Anemia (73%)**** • Neutropenia • Thrombocytopenia

* Part of the CRAB Criteria

Kyle RA, et al. (2003). *Mayo Clin Proc* 78(1):21-33.

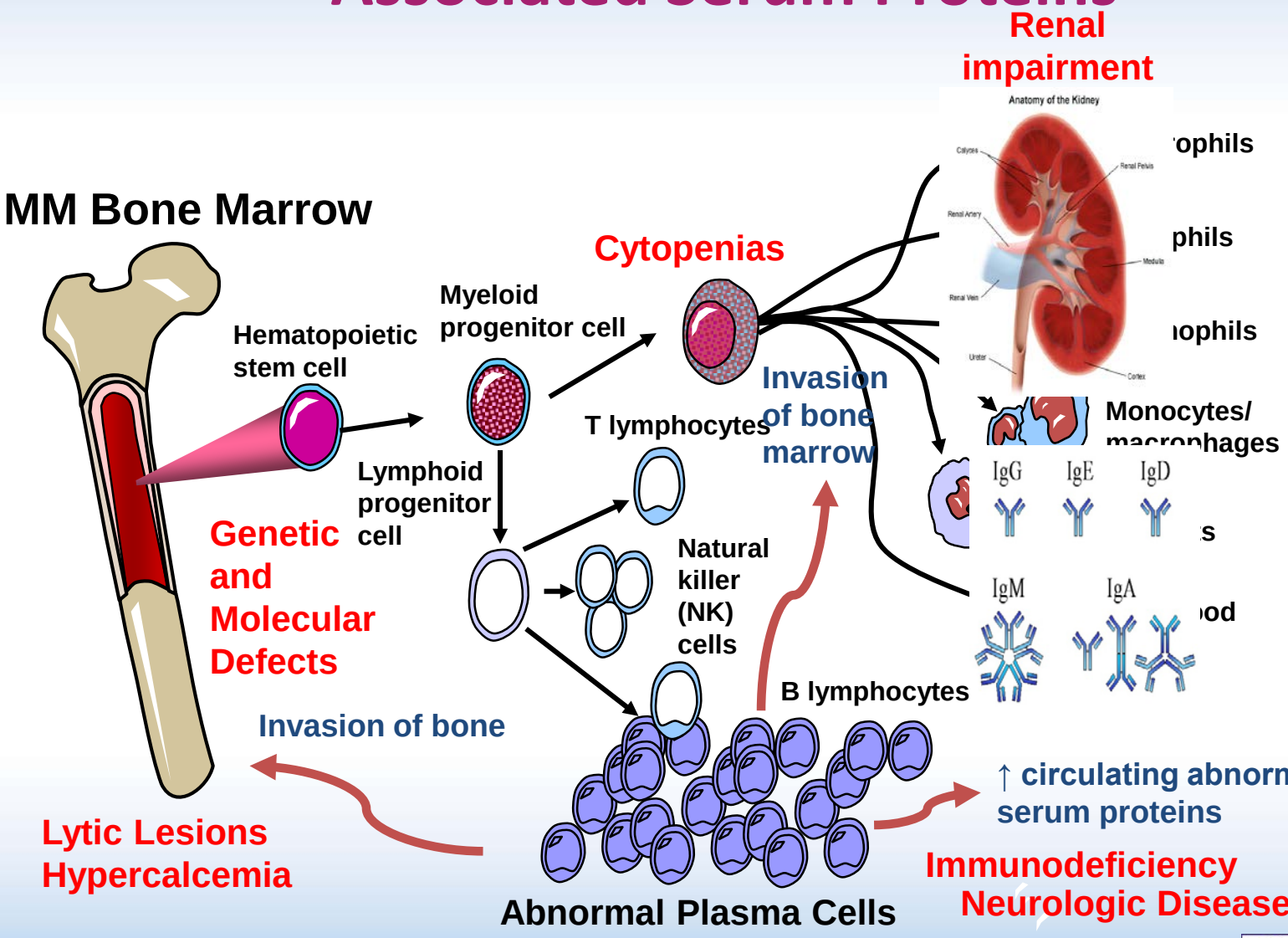
Common Presenting Signs and Symptoms (cont.)

Disease Process	Symptoms	Clinical Findings
Renal injury	• Fatigue • Oliguria (late finding) • Hematuria	• ***Elevated creatinine (19%)**** • Acute renal failure (ARF) • Chronic renal insufficiency (CRI) • Chronic renal failure • Anemia • Hypercalcemia • Hyperviscosity • Urate nephropathy
Abnormal immunoglobulin function	• Fever • Infections	• Hypogammaglobulinemia • Infections • Neurologic disease
Hyperviscosity	• Pain • Paresthesia • Immobility	• Peripheral neuropathy (5%) • Strokes

* Part of the CRAB Criteria

Kyle RA, et al. (2003). *Mayo Clin Proc* 78(1):21-33.

Overproduction of Abnormal Plasma Cells and Associated Serum Proteins

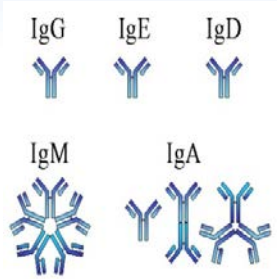


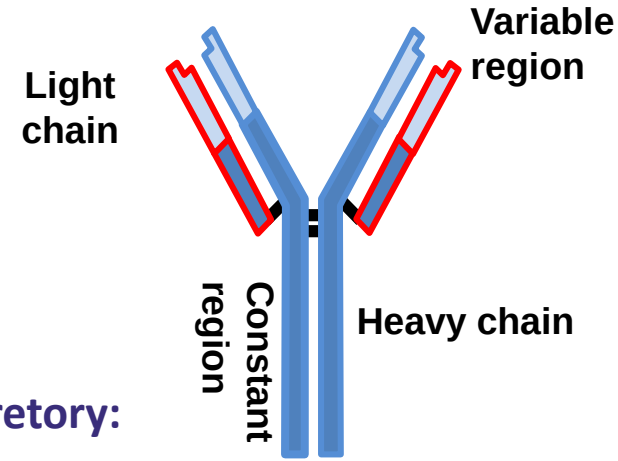
Stem cell basics. NIH Stem Cell Information. Available at: http://stemcells.nih.gov/info/basics/basics4.asp. Accessed June 4, 2013. Image created by Sandy Kurtin, The University of Arizona Cancer Center.

Classification of MM

Heavy chain:

- IgG, IgA, IgD, IgM, IgE
- 77% of myeloma cases
- IgG and IgA most common



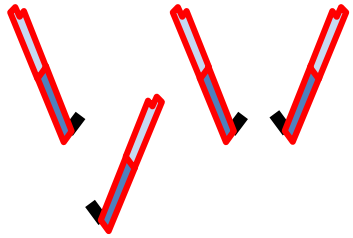


Nonsecretory:

- No detectable immunoglobulin
- 1% to 2% of myeloma cases

Light chain (Bence-Jones protein):

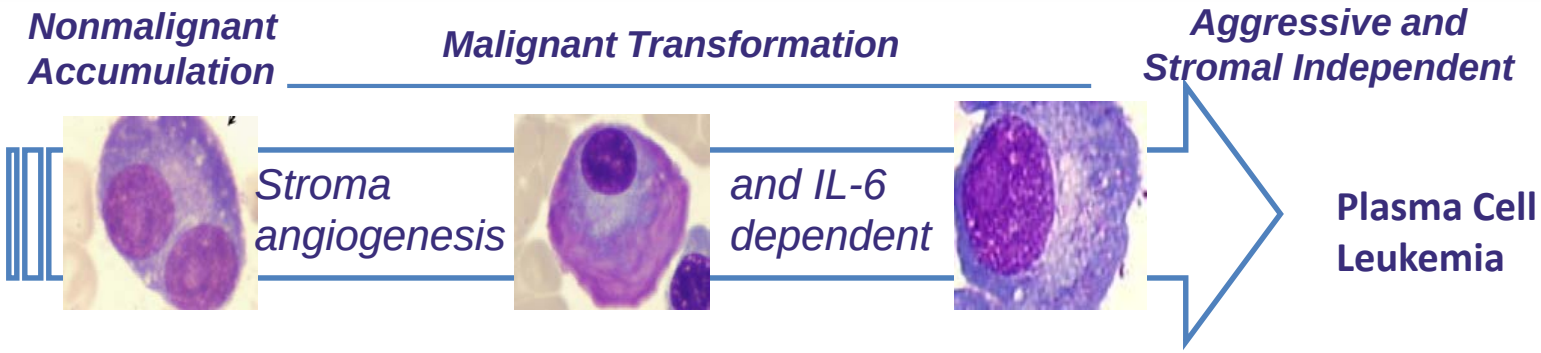
- Kappa (κ) or lambda (λ)
- 20% of myeloma cases



Serum free light chain

Kumar SK, et al. (2009). *Mayo Clinic Proc*. 84:1095-1110; Schmidt-Hieber M, et al. (2013). *Haematologica*. 98:279-287.

Disease Trajectory



MGUS	Smoldering Myeloma	Multiple Myeloma
▪ < 10% BMPC ▪ <30g/L M-protein ▪ No MDE ▪ 1%/yr risk of progression to MM	▪ 10-60% BMPC ▪ ≥ 30g/L M-protein (igG or IgA) OR • ≥ 500 mg/24 hr urinary protein ▪ No MDE or amyloidosis ▪ 10%/yr risk of progression to MM in the first 5 yr	≥ 10% clonal BMPC or biopsy proven bony or extramedullary plasmacytoma AND 1 or more Myeloma Defining Events (MDE) including CRAB features. Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically

Rajkumar, et al., 2014; Kuehl WM, et al. (2002). *Nat Rev Cancer*. 2:175-187. Agarwal A, et al. (2013). *Clin Cancer Res*.19:985-994. Durie BG, et al. (2003). *Hematol J*. 4:379-398. Kurtin SE. (2010). *J Adv Pract Oncol*. 1:19-29.

Myeloma Defining Events (MDEs): CRAB Criteria Revised

C: Calcium elevation

Serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than ULN or
> 2.75 mmol/L (> 11 mg/dL)

R: Renal dysfunction

Creatinine clearance < 40 mL/min or
serum creatinine > 177 µmol/L (> 2 mg/dL)

A: Anemia

Hemoglobin > 20 g/L below LLN or < 100 g/L

B: Bone disease

One or more osteolytic lesions on skeletal radiography, CT, or PET/CT

Any one or more biomarkers of malignancy

- BMPC > 60%
- Involved/uninvolved serum free light chain ratio ≥ 100
- > 1 focal lesion > 5 mm on MRI studies

MGUS = myeloma of undetermined significance; SMM = smoldering multiple myeloma; BMPC = bone marrow plasma cells; MDE = myeloma-defining events; ULN = upper limit of normal; LLN = lower limit of normal. From Kurtin et al., 2016, *J Adv Pract Oncol*; Adapted from Rajkumar et al., 2014, *Lancet Oncol*, 15(2):e538-e54.

Case Study 1

- 57-yr-old male presented to PCP with intractable back pain over 2-week period
  - Prior discectomy treated with nonsteroidal pain medication; no improvement
- Presented to ED on weekend with severe pain
  - Plain films of spine and pelvis showed degenerative changes
  - CT of spine (bone protocol) with osseous demineralization and a moth-eaten appearance of bones
- Labs
  - WBC 5.5 g/dL, hemoglobin 11.7 g/dL, hematocrit 34%, platelets 240,000/µL
  - Creatinine 2.6 mg/dL, calcium 12.8 mg/dL, albumin 3.4 g/dL
- Admitted with acute renal failure and hypercalcemia
- Suspicion for multiple myeloma: consult to hematology/oncology

Initial Workup

General

- H&P with particular attention to bone health, fatigue, infections, neuropathy
- Co-morbidity evaluation
- Fit vs. frail
- Lifestyle and personal wishes
- Financial considerations
- Availability of a caregiver

Peripheral Blood

- CBC, differential, and platelet count
- CMPNL: Includes BUN, creatinine, calcium, albumin
- B_2 microglobulin
- LDH
- FLC assay+
- SPEP with IFE
- Quantitative Immunoglobulins
- 24 hour urine: UPEP with IFE

Initial diagnostic evaluation of suspected multiple myeloma (NCCN, 2010). BUN = blood urea nitrogen; CBC = complete blood cell count; FISH = fluorescence in situ hybridization; Ig = immunoglobulin; LDH = lactate dehydrogenase; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRI = magnetic resonance imaging.

Kurtin et. al. (2016*) J Adv Pract Oncol*, 7(S1), S59-S70. Adapted from: Kurtin, 2010. Data from: NCCN, 2015, Ludwig et al., 2014; Rajkumar et al, 2014, Mikhael, et al., 2013

Imaging Techniques for Assessing Bone Disease

Technique	How it Works	When to Use	Limitations to Use
WBXR/bone survey	• Series of x-rays of axial and appendicular skeleton	• Baseline & relapse	• Bone lesions only seen if >30% bone loss occurs • More accurate for lesions in the ribs and skull than newer techniques
MRI	• Three sequence approach (T1,T2, STIR, post-gadolinium) detects MM activity in bone marrow • Highly sensitive	• Procedure of choice to evaluate a painful lesions • Verify solitary plasmacytomas; non-secretory disease • Assess spinal cord compression	• Lack of specificity reflects marrow infiltration not specifically bone deterioration • Expense & time • Excludes patients with implanted metal

STIR = short time inversion recovery; FDG = 18-fluorine-fluoro-deoxyglucose ; MRD = minimal residual disease
CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography;
DEXA = dual-energy X-ray absorptiometry; MM = multiple myeloma.
Dimopoulos, Hillengass et al. 2015; Regelink, Minnema et al. 2013, Dimopoulos, Kyle et al. 2011, NCCN, 2016

Imaging Techniques for Assessing Bone Disease (cont'd)

Technique	How it Works	When to Use	Limitations to Use
CT	• Multiple computerized x-ray images from different angles • Highly sensitive	• Early detection of bone lesions not detected by WBXR • More sensitive to detect small osteolytic lesions	• Does not differentiate between active & inactive lesions • Higher levels of radiation exposure
PET	• FDG tracer illuminates metabolically active cells • Highly sensitive	• Assess extra-medullary disease; response; MRD	• Lack of specificity of findings may result in false-positive results; expense
DEXA (bone densitometry)	• Measurement of osteopenia or osteoporosis	• If comorbid conditions exist for osteoporosis	• Does not measure osteolytic disease

STIR = short time inversion recovery; FDG = 18-fluorine-fluoro-deoxyglucose ; MRD = minimal residual disease
CT = computed tomography; MRI = magnetic resonance imaging; PET = positron emission tomography;
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Dimopoulos, Hillengass et al. 2015; Regelink, Minnema et al. 2013, Dimopoulos, Kyle et al. 2011, NCCN, 2016)

Case Study (cont'd)

- 57-yr-old male, excellent performance status
- PMH/comorbidities
  - Bladder cancer, hyperlipidemia, hypertension, basal cell carcinoma, melanoma, shingles, anxiety, insomnia, colon polyp
  - Exposure to trichlorethylene in childhood
- Medications
  - Gabapentin (post-herpetic neuralgia), diazepam, hydrocodone, acyclovir
- Social
  - Retired engineer, married, 2 sons
  - No tobacco history, occasional alcohol

Case Study (cont'd)

Imaging

- Skeletal survey
  - Degenerative changes of lumbar spine, otherwise normal exam (lesions noted on CT not apparent)
- Renal ultrasound
  - No renal parenchymal disease
- PET/CT
  - Subtle lytic changes within thoracic and lumbar vertebral bodies; mildly hypermetabolic; max SUV 2.8

Bone marrow

- 9.58% monotypic plasma cells
- FISH: del(13q); loss of 3-IGH of chromosome 14, trisomy 15; del(17p)
- Cytogenetics: normal male karyotype

Case Study (cont'd)

Peripheral blood

Serum free light chains

- Kappa: 338 mg/dL (0.33-1.94 mg/dL)
- Lambda: 0.21 mg dL (0.57-2.63 mg/dL)
- Ratio: 1012.50 (0.26-1.65)
- β_2M: 2.58 mg/L
- LDH: 249 IU/L
- C-reactive protein: 12.30 mg/L
- SPEP: no monoclonal protein

UPEP

- M-component: 606 mg/L (normal = 0)
- Immunofixation of urine demonstrates multiple oligoclonal bands in kappa lane

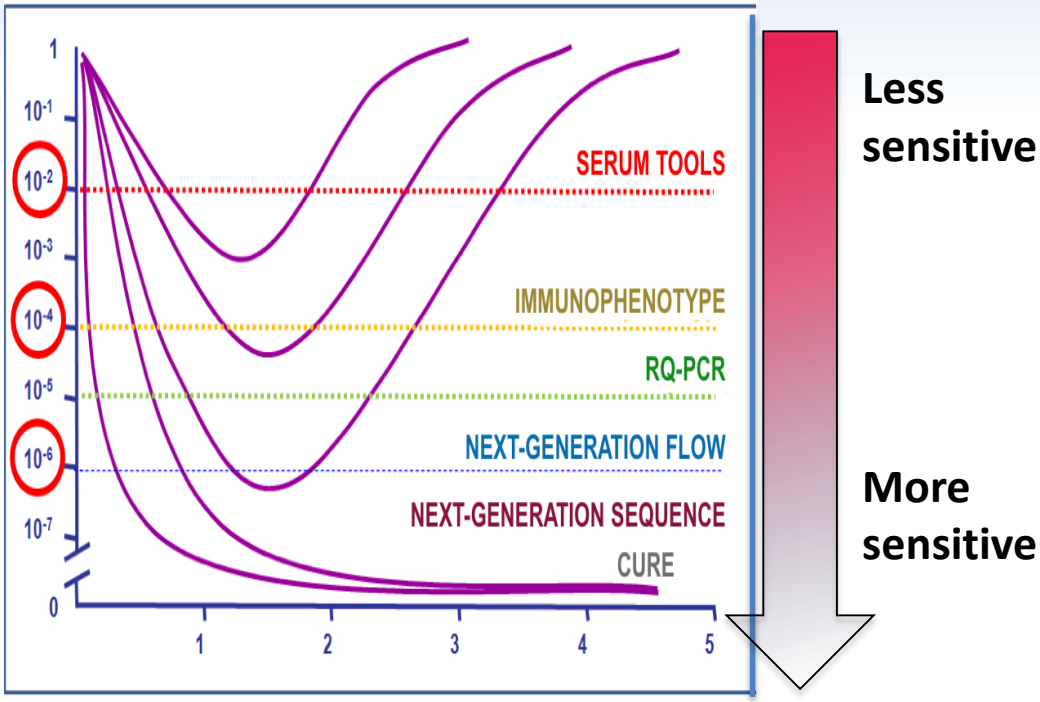
Updated MM Staging

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta 2 microglobulin < 3.5 mg/dL Serum albumin ≥ 3.5 g/dL Median survival: 62 months	ISS stage I and standard risk chromosomal abnormalities by iFISH – ***AND*** Serum LDH < ULN (varied by institution) 5 year OS rate: 82%; PFS at 46 months 55%
II	Not ISS stage I or II Median survival: 44 months	Not R-ISS stage I or III 5 year OS rate: 62%; PFS at 46 months 36%
III	Serum beta-2 macroglobulin greater than or equal to 5.5 mg/L Median survival: 29 months	ISS stage III and either high risk chromosomal abnormalities by iFISH ***OR*** Serum LDH > ULN (varied by institution) 5 year OS rate: 40%; PFS at 46 months 24%

Greipp et al. (2005). *J Clin Oncol*. 23:3412-3420; Palumbo, A., et al. (2015). *J Clin Oncol.* 33:2863–2869

Minimal Residual Disease: The Path to a Cure

- MRD is becoming a standard endpoint for assessing outcome
- Next generation flow (NGF) is part of the new response criteria
- MRD status does not tell us whether to change therapy, continue therapy, or stop therapy
- It can be used as a prognostic marker more than a tool for treatment decisions



- A patient negative for MRD by less-sensitive assay may truly be positive for MRD
- Next-generation sequencing (NGS) and next-generation flow (NGF) are becoming standard tools for assessing MRD

Brian Durie, Best of ASH 2014. Available at http://myeloma.org/ArticlePage.action?articleId=4492

General Approach to Treatment of NDMM

Confirmed Diagnosis of Multiple Myeloma: MDE and CRAB Criteria

Determination of transplant eligibility

Immediate interventions for serious adverse events

Individualized Treatment Selection for Induction Therapy

Transplant Eligible

Works rapidly (CR, nCR, VGPR)
Well tolerated
Spares stem cells
Level of evidence 1 or 2A

Transplant Ineligible

Achieving a CR or nCR
Level of evidence 1 or 2A
Tolerability and QOL
Fit vs. frail and comorbidities

Continued Treatment

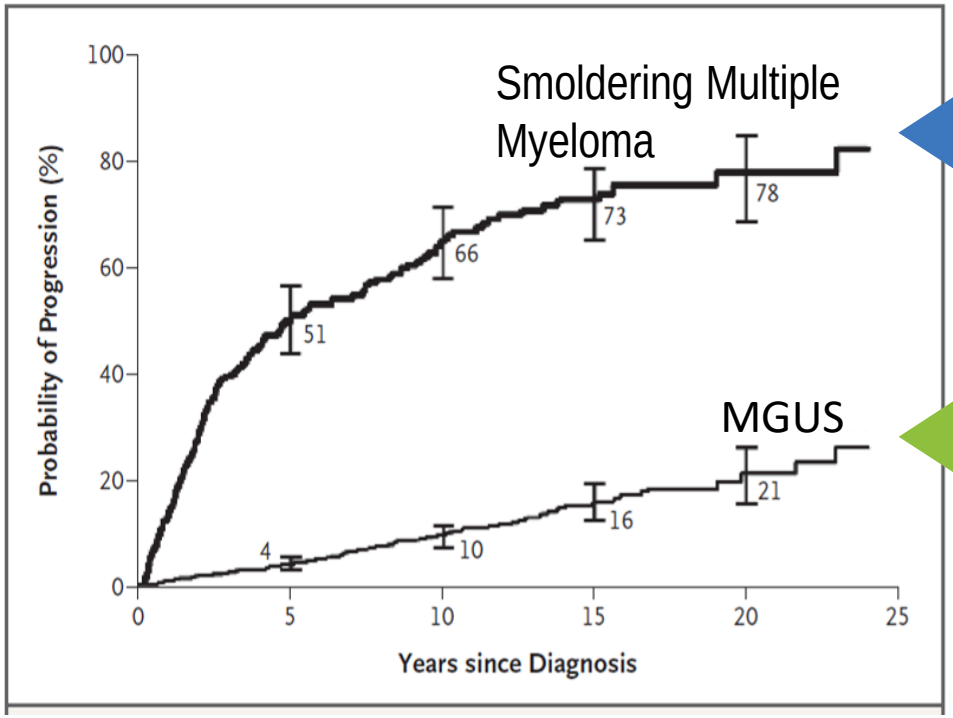
Salvage therapy

Maintenance therapy

NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.3.2016.

Smoldering Multiple Myeloma Patients Have a High Risk of Progression

Disease Progression in SMM and MGUS Patients



10% risk of progression per year*

- Screen every 4 to 6 weeks

*For first 5 years, ~3% per year for next 5 years, ~1% per year thereafter

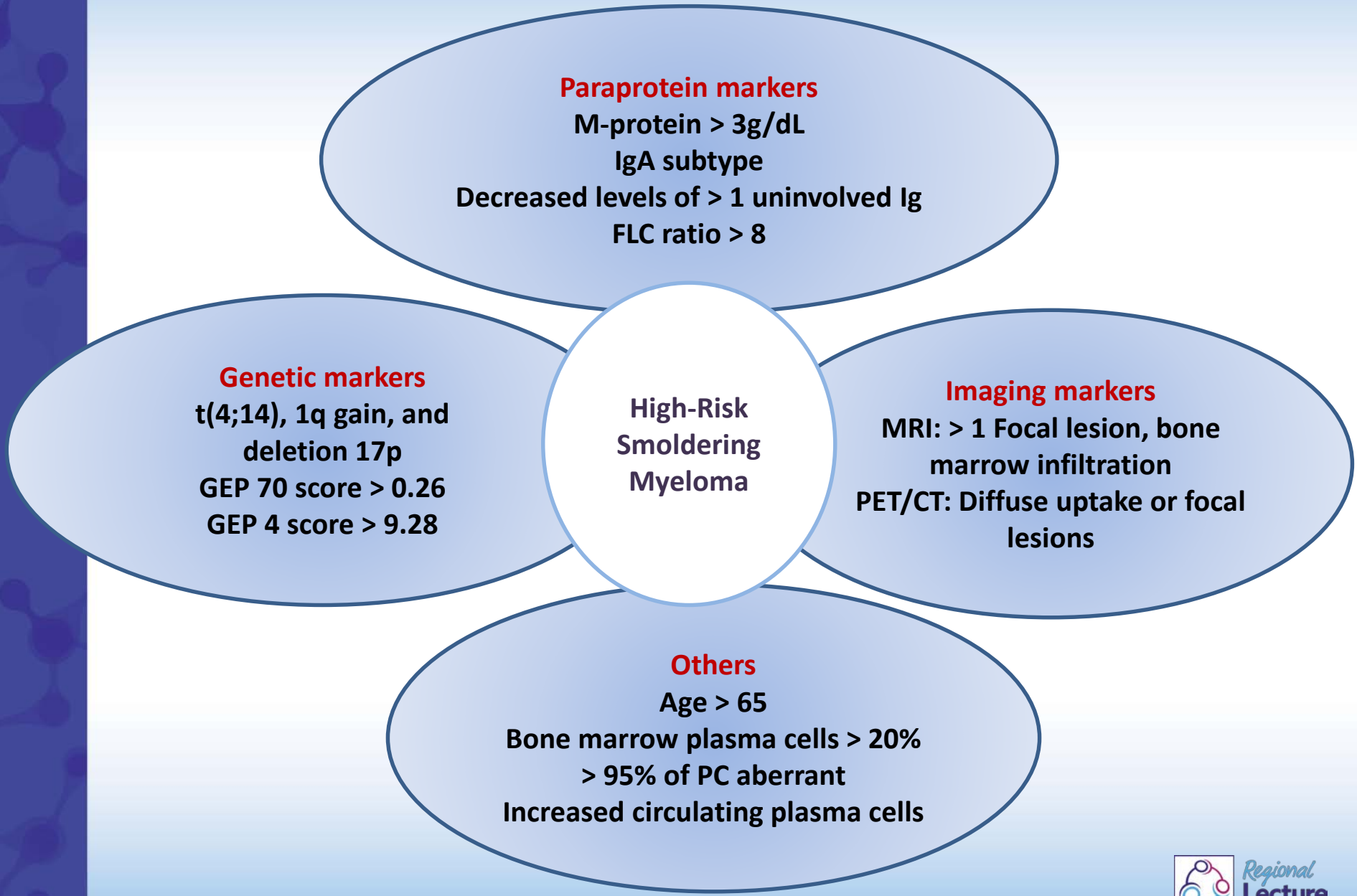
1% risk of progression per year

- First year: screen every 3 to 6 months
- After first year: screen at least every 1 to 2 years
- 3% of people over 50 years old
- 5% of people over 70 years old

SMM = smoldering multiple myeloma
MGUS = monoclonal gammopathy of undetermined significance

Kyle RA, et al. *N Engl J Med.* 2007;356:2582-2590; Jagannath S, et al. *Clin Lymphoma Myeloma Leuk.* 2010;10(1):28-43; Kyle RA, et al. *Curr Hematol Malig Rep*. 2010 ;5(2):62-69; Rajkumar et al., 2014, *Lancet Oncol* 15(12), e538-e548.

Factors Associated With High-Risk Smoldering MM



Sundararajan et al., 2016, published online *Curr Hematol Malig Rep*, DOI10.1007/s11899-016-0305-6

Cytogenetic Classification

- mSMART 2.0: classification of active MM

High Risk 20%	Intermediate Risk 20%	Standard Risk 60%
▪ FISH – Del17p – t(14;16) – t(14;20) ▪ GEP – High-risk signature	▪ FISH – t(4;14) ▪ Cytogenetic deletion 13 or hypodiploidy ▪ PCLI ≥ 3%	All others including: ▪ Hyperdiploid ▪ t(11;14) ▪ t(6;14)
OS 3 Years	**OS 4-5 Years**	**OS 8-10 Years**

Mikhael JR, et al. *Mayo Clinic Proc*. 2013;88:360-376.

Other Biomarkers Associated With High-Risk MM

Biomarker	2-yr probability of progression
High levels of circulating plasma cells	80%
Abnormal plasma cell immunophenotype ≥95% plus immunoparesis	50%
Evolution of smoldering multiple myeloma	65%
Cytogenetic subtypes: t (4;14), 1q amp, or del 17p	50%
High bone marrow plasma cell proliferative rate	80%
Unexplained decrease in creatinine clearance by ≥25% accompanied by a rise in urinary monoclonal protein or serum free light-chain concentrations	Not known

*Increase in serum monoclonal protein by ≥10% on each of two successive evaluations within a 6-month period

Rajkumar, S. V., et al. (2014) *The Lancet Oncology* **15**(12): e538-e548

Mayo Clinic Approach to Newly Diagnosed MM

***NOTE*: Clinical trial participation should be encouraged.**

Standard Risk	Intermediate Risk	High Risk
VRD for 4 cycles*	VRD for 4 cycles*	KRD for 4 cycles
ASCT in eligible patients; if ineligible, continue VRD for 12 cycles; if frail or aged ≥75 yr, continue Rd	ASCT in eligible patients; if ineligible, continue VRD for 12 cycles; if frail or aged ≥75 yr, consider low-dose VCD	ASCT in eligible patients; if ineligible, continue VRD for 12 cycles; if frail or aged ≥75 yr, consider lower doses
Lenalidomide maintenance if not in CR or VGPR following ASCT	Bortezomib or bortezomib-based maintenance for 2 yr	Carfilzomib or bortezomib-based maintenance for 2 yr

Mikhael JR, et al. *Mayo Clinic Proc*. 2013;88:360-376.

Factors Affecting Transplant Eligibility

- Age
  - Older than 70 yrs of age may not be eligible
  - Older pts more sensitive to toxicity; less physical reserve
- Fit vs. frail
- Comorbidities: heart disease, lung disease
  - Increased risk of infection
  - Decreased tolerability for high-dose therapy
- Renal and hepatic function
- Personal preference
- Insurance coverage
- Eligibility of a caregiver

NCCN. Clinical practice guidelines in Oncology: Multiple Myeloma. v.3.2016.; Miceli et al., 2013, Clin J Oncol Nurs 17 Suppl, 13-24

Case Study: Transplant Eligibility

- Individual patient considerations
  - Prior history of cancer
    - Bladder; resected (cure)
    - Basal cell; resected (cure)
    - Melanoma; resected (cure)
    - Polyp; hyperplastic
  - TCE exposure in childhood
  - Anxiety
  - Married
  - Retired engineer
- MM-specific considerations
  - Risk-stratification is critical to early treatment decisions
  - Multiple treatment options
  - High-risk disease (del17p)
- Consideration of HSCT
  - Excellent performance status
  - Availability of caregiver; supportive family and friends
  - Good organ function

FDA Approved Drugs to Treat MM

Drug	Abbreviation	Drug Class	Brand
Bortezomib	btz	Proteasome inhibitor	Velcade
Carfilzomib	car	Proteasome inhibitor	Kyprolis
Daratumumab	dara	Monoclonal antibody	Darzalex
Elotuzumab	elo	Monoclonal Antibody	Emplicit
Lenalidomide	len	Immunomodulatory agent	Revlimid
Ixazomib	Ixa	Proteasome inhibitor	Ninlaro
Thalidomide	thal	Immunomodulatory agent	Thalomid
Pomalidomide	pom	Immunomodulatory agent	Pomalyst
Panobinostat	pan	Histone deacetylase inhibitor	Farydak
Melphalan	mel	Alkylating agent	Alkeran, Alphalan
Cyclophosphamide	CTX	Alkylating agent	Cytoxan
Prednisone	P, pred	Corticosteroid	Deltasone
Dexamethasone	D, d, dex, DXM	Corticosteroid	Decadron
Pamidronate	pmd	Bisphosphonate	Aredia
Zoledronic acid	zol	Bisphosphonate	Zometa

NCCN Preferred Regimens - Category 1

Myeloma Preferred Induction Regimens*		
	Combination	Abbreviation(s)
Transplant	Bortezomib/dexamethasone (dex)†	VD or Vd
	Bortezomib/cyclophosphamide/dex	CyBorD
	Bortezomib/doxorubicin/dex†	
	Bortezomib/lenalidomide/dex	VRD or VRd
	Bortezomib/thalidomide/dex†	VTD or VTd
	Lenalidomide/dexamethasone†	RD or Rd
Non-transp.	Bortezomib/dex	VD or Vd
	Lenalidomide/low-dose dex†	Rd
	Bortezomib/cyclophosphamide/dex	
	Bortezomib/lenalidomide/dex	
	Bortezomib/thalidomide/dex†	VMP or MPB
	Lenalidomide/dexamethasone†	MPR or MPL
	Melphalan/prednisone/thalidomide†	MPT

Combination therapies have demonstrated improved response rates, progression-free survival, and/or overall survival compared to single agents

Supportive and palliative care should be provided concurrently with disease modifying treatment bisphosphonates, antibiotics, and reduced doses of steroids

Improving quality of life and survival has become an important goal of treatment

*NCCN Guidelines Multiple Myeloma Version 3.2016
†Category 1

Immunomodulatory Agents

Agent/Class	Dosing and Route of Administration
Lenalidomide[1] Immunomodulatory agent	▪ 25 mg/day by mouth for induction ▪ Variable dosing in combination regimens ▪ Dose modification based on renal function, cytopenias
Pomalidomide[2] Immunomodulatory agent	▪ 4 mg/day on days 1-21 using a 28-day cycle ▪ Dose modifications for cytopenias
Thalidomide[3] Immunomodulatory agent	▪ 50-200 mg/day by mouth at bedtime ▪ Variable dosing in combination regimens ▪ Dose modification for neuropathy, cytopenias

1. Lenalidomide [package insert]. 2. Pomalidomide [package insert]. 3. Thalidomide [package insert].

Proteasome Inhibitors

Agent	Dosing and Route of Administration
Bortezomib[1]	▪ 1.3 mg/m^2 IV or SC on days 1, 4, 8, 11, every 21 days x 2 cycles, then weekly dosing 3 wks on/1 wk off ▪ Variable dosing as a single agent and in combination regimens ▪ Dose modification for neuropathy, cytopenias
Carfilzomib[2]	▪ 20 mg/m^2 IV (cycle 1), 27 mg/m^2 (cycles 2-12) on Days 1, 2, 8, 9, 15, 16, every 28 days ▪ Dose modifications for cytopenias, cardiopulmonary symptoms
Ixazomib[3]	▪ Recommended starting dose of 4 mg taken orally on days 1, 8, and 15 of a 28-day cycle ▪ Dose should be taken at least 1 hour before or at least 2 hours after food ▪ Dose modification for moderate or severe hepatic impairment, or renal impairment

1. Bortezomib [package insert]. 2. Carfilzomib [package insert]. 3. Ixazomib [package insert]

Clinical Considerations in Induction Therapy

For induction therapy in transplant eligible patients, triple therapy is recommended with VRd as the recommended initial regimen

- **High tumor burden**
  - Pulse dexamethasone
  - Combination therapies with alkylators and IMiDS and bortezomib
- **Renal failure**
  - Pulse dexamethasone
  - Proteasome Inhibitor +/- alkylator
  - Renal dosing required for selected agents - may benefit from graduated induction
- **Hypercalcemia**
  - Pulse dexamethasone
  - Bisphosphonates
  - Risk-adapted induction
- **Frail**
  - Avoid high-dose dexamethasone
  - Dose modifications may be indicated for selected agents
- **Clotting or bleeding history**
  - Assess risk of use of IMIDs
  - Evaluate platelet function with concurrent use of anticoagulation/ anti-platelet agents
- **Preexisting neuropathy**
  - Assess use of bortezomib/ thalidomide

Niesvizky R, et al. Oncology (Williston Park). 2010;24:14-21; NCCN. Clinical practice guidelines in oncology: multiple myeloma. v.3.2016. ; Stadtmauer EA. Oncology (Williston Park). 2010;24:7-13.

Expected Side Effects of Front-Line Therapies: IMiDs

Side effect	Thalidomide	Lenalidomide	Pomalidomide
Peripheral neuropathy	√		
Deep vein thrombosis	√ More with dex	√ More with dex	√ More with dex
Myelosuppression	√ Neutropenia	√ Neutropenia, thrombocytopenia, anemia	√ Neutropenia, thrombocytopenia, anemia
Fatigue, weakness	√	√	√
Sedation	√		
Rash	√	√	√
Gastrointestinal disturbance	√ Constipation	√ Constipation, diarrhea	√ Constipation, diarrhea
Renal/Hepatic		√ Reduce dose for decreased CrCL	

CrCL, creatinine clearance; dex, dexamethasone; len, lenalidomide.
Velcade prescribing information; Revlimid prescribing information; Thalomid prescribing information; Pomalyst prescribing information; Kyprolis prescribing information.

Expected Side Effects of Front-Line Therapies: Proteasome Inhibitors

Side effect	Bortezomib	Carfilzomib	Ixazomib
Peripheral neuropathy	√		
Myelosuppression	√ Thrombocytopenia	√ Neutropenia, thrombocytopenia, anemia	√ Neutropenia, thrombocytopenia, anemia
Hypotension	√		
Cardio/Pulmonary	√	√	√ ECG abnormalities
Fatigue, weakness	√	√	
Viral reactivation of herpes zoster	√	√	√
Gastrointestinal disturbance	√ Nausea and vomiting, diarrhea	√ Nausea and vomiting, diarrhea, constipation, mucositis/stomatitis	√ Diarrhea
Renal/Hepatic	√ Hepatic		

CrCL = creatinine clearance; dex = dexamethasone

Velcade prescribing information; Revlimid prescribing information; Kyprolis prescribing information.

SWOG S0777: Newly Diagnosed MM

Study Design

Randomized phase III trial of VRd vs. Rd in previously untreated active MM

- **VRd x eight 21-day cycles**
  - **Len 25 mg/d; dex 40 mg weekly**
  - **n = 230**
- **Rd x six 28-day cycles**
  - **Len 25 mg, dex 20 mg 2 consecutive days each week**
  - **n = 243**
- **Followed by: Rd maintenance until PD, unacceptable toxicity, or withdrawal of consent**

Outcomes

- **Primary end point: PFS**
- **Secondary end points: ORR, OS, safety**

Timeline:

- **Median follow-up: 55 mo; median time on maintenance: 385 days**

Prophylaxis

- **All pts received aspirin 325 mg/day; bortezomib pts received HSV prophylaxis**

Durie B, et al. ASH 2015. Abstract 25.

SWOG S0777: Key Takeaways

VRd induction followed by continuous Rd maintenance represents potential new standard of care for newly diagnosed MM

PFS

OS

Safety

Survival (mo)	VRd (n = 242)	Rd (n = 229)	HR	*P* Value
Median PFS	43	30	0.712 (0.560 - 0.906)	.0018*
Median OS	75	64	0.709 (0.516 - 0.973)	.025†

Adverse Event,* %	VRd (n = 241†)	Rd (n = 226†)	*P* Value
Grade ≥ 3 AE			
▪Neurologic	33	11	< .0001
▪Pain	12	4	.0002
▪Sensory	23	3	.004
▪Gastrointestinal	22	8	NR
Secondary primary malignancies	4	4	

Durie B, et al. ASH 2015; Abstract 25.

IFM/DFCI 2009: Phase III, Randomized Symptomatic, Newly Diagnosed MM Patients (N = 700)

Study design

- Pts 65 yrs of age or younger with symptomatic, measurable NDMM
- RVd x 8 followed by Rd maintenance
  - RVd: bortezomib 1.3 mg/m^2 IV on days 1, 4, 8, 11 + lenalidomide 25 mg on days 1-14 + dexamethasone 20 mg on days 1, 2, 4, 5, 8, 9, 11, 12

  VS
  - RVd x 3 -> cyclophosphamide mobilization -> MEL200 + HSCT -> R maintenance

Outcomes

- Primary objective: PFS
- Secondary objectives: ORR, MRD, TTP, OS, safety

Attal M, et al. ASH 2015. Abstract 391.

IFM/DFCI 2009: Phase III, Randomized Symptomatic, Newly Diagnosed MM Patients (N = 700): Key Takeaways

Despite a very effective regimen such as VRd, adding transplantation as a part of the continuum of therapies certainly seems to increase the depth of response, and these patients do well

PFS

OS

Parameter	RVd (n = 350)	Transplantation (n = 350)	*P* Value
Median follow-up, mo	41	41	
Progression or death, n	204	158	
Median PFS, mo	34	43	
4-yr PFS, %	35	47	
HR (95% CI)	1	0.69 (0.56-0.84)	< .001
4-yr survival, %	83	81	
HR (95% CI); P value		1.2 (0.7-1.8); NS	

Attal M, et al. ASH 2015. Abstract 391.

IFM/DFCI 2009: Phase III, Randomized Symptomatic, Newly Diagnosed MM Patients (N = 700): Key Takeaways

Despite a very effective regimen such as VRd, adding transplantation as a part of the continuum of therapies certainly seems to increase the depth of response, and these patients do well.

Safety

Event, %	RVd (n = 350)	Transplantation (n = 350)
Neutropenia	31	89
Thrombocytopenia	9	78
Infection	10	18
Thromboembolic events	4	5
Peripheral neuropathy	11	11
Secondary primary malignancies	3	5

Attal M, et al. ASH 2015. Abstract 391.

IFM/DCFI 2009: Overall Conclusions

- ASCT vs. RVD in pts with NDMM is associated with:
  - 31% reduced risk of progression or death ($P < .001$)
  - Improved TTP and rate of MRD negativity
  - Similar, low rate of mortality
- Longer follow-up required to make any conclusions about OS
- ASCT should remain a standard of care for eligible pts with myeloma
- Similar, confirmatory trial ongoing in US

Attal M, et al. ASH 2015. Abstract 391.

MRD Sub-studies of IFM/DFCI 2009

MRD Assessment

- Bone marrow MRD evaluation planned before and after maintenance for pts achieving ≥ VGPR in either arm
- Primary objective: assess MRD by FCM
- Secondary objective: assess MRD by NGS (n = 289)

Imaging (IMAJEM) Sub-study

Evaluation of Imaging, MRD and survival based on imaging

- MRI or PET/CT at diagnosis
- MRI or PET/CT after 3 cycles of RVD
- MRI or PET/CT before maintenance

NGS = next generation sequencing; MRD = minimal residual disease

Avet-Loiseau H, et al. ASH 2015. Abstract 191; Moreau P, et al. ASH 2015. Abstract 395.

MRD Sub-studies of IFM/DFCI 2009

MRD Assessment

- MRD-negative status significantly predictive of 3-yr PFS
- NGS offers improved MRD sensitivity (< 10-6) over FCM and is feasible in most pts
- MRD negativity at 10-6 level strongly predictive of 3-yr PFS, including pts who achieve CR and those with t(4;14) and in both treatment arms
- Investigators concluded:
  - Sensitive MRD evaluation may identify pts cured of myeloma
  - Warrants further evaluation in clinical trials

Imaging (IMAJEM) Sub-study

- PET/CT and MRI both effective in detecting bone lesions at diagnosis
- MRI negativity was not prognostic for PFS, OS during follow-up
- PET/CT negativity after 3 cycles of chemotherapy and before maintenance is prognostic for PFS
- PET/CT negativity before maintenance is prognostic for OS
- PET/CT and flow cytometry can be complementary when evaluating MRD status

Avet-Loiseau H, et al. ASH 2015. Abstract 191; Moreau P, et al. ASH 2015. Abstract 395.