Understanding Multiple Myeloma, Its Treatment, and New Discoveries: Part 2

Presented as a Live Webinar

Wednesday, August 19, 2015

1:00 p.m. – 2:00 p.m. EDT

On-demand Activity

Live webinar recorded and archived to be watched at your convenience

Available after October 1, 2015

www.ashpadvantage.com/multmyeloma

Planned by ASHP Advantage and supported by an educational grant from Onyx Pharmaceuticals Inc., a subsidiary of Amgen Inc.

Activity Overview

This educational activity will review the management of patients with multiple myeloma with refractory disease and how to apply supportive care strategies. New therapies in development that have the potential to radically change the treatment and clinical course of the disease will also be discussed. Patient case scenarios will be used to highlight decision points in managing patients with multiple myeloma.

Learning Objectives

At the conclusion of this application-based educational activity, participants should be able to

- Evaluate treatment regimens for patients with relapsed, refractory multiple myeloma.
- Illustrate strategies for addressing the supportive care needs of patients with multiple myeloma who experience adverse reactions or develop complications.
- Examine how current approaches to the treatment of multiple myeloma may evolve based on recent clinical trial data and new treatment discoveries.

List of Abbreviations

For a list of abbreviations used in the activity, please see pages 23-24.

Continuing Education Accreditation

ASHP is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This activity provides 1.0 hour (0.1 CEU – no partial credit) of continuing pharmacy education credit (ACPE activity #0204-0000-15-453-L01-P for the live activity and ACPE activity #0204-0000-15-453-H01-P for the on-demand activity).

Participants will process CPE credit online at http://elearning.ashp.org/my-activities. CPE credit will be reported directly to CPE Monitor. Per ACPE, CPE credit must be claimed no later than 60 days from the date of the live activity or completion of a home-study activity.

Webinar Information

Visit www.ashpadvantage.com/multmyeloma to find

- Webinar registration link
- Group viewing information and technical requirements
- CPE webinar processing information

Additional Educational Activities

- On-demand activities based on Part 1 and Part 2 live webinars (1 hour CPE for each activity, available after October 1, 2015) – Please note that individuals who claim CPE credit for the live webinar are ineligible to claim credit for the on-demand activity

www.ashpadvantage.com/multmyeloma

Activity Faculty

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Dr. Fausel received his Bachelor of Science degree in pharmacy and Doctor of Pharmacy degree from Albany College of Pharmacy in Albany, New York. He completed an ASHP-accredited pharmacy practice residency at Samuel S. Stratton VA Medical Center in Albany, New York. More recently, he earned a Master of Health Administration degree from Simmons College in Boston, Massachusetts.

Dr. Fausel is the founding Residency Program Director for the postgraduate year two (PGY-2) oncology pharmacy residency at Indiana University Health. He chairs two Institutional Review Boards (IRBs) for Indiana University and serves on the IRB Executive Committee for the university.

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Dr. Harvey received his Bachelor of Science in Pharmacy and Doctor of Pharmacy degrees from the University of North Carolina (UNC) in Chapel Hill. He subsequently completed a pharmacy practice residency at the University of Kentucky Medical Center and College of Pharmacy and a hematology/oncology specialty residency at UNC Hospitals and School of Pharmacy.

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Disclosure Statement

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- R. Donald Harvey, Pharm.D., FCCP, BCOP, declares that he has served as an advisor for Bristol-Myers Squibb, Onyx Pharmaceuticals Inc., and Takeda Pharmaceuticals. He has also participated in research activities funded by Acetylon Pharmaceuticals, Inc.; Bristol-Myers Squibb; Calithera Biosciences; Celgene Corporation; Cleave Biosciences; Novartis Pharmaceuticals; Onyx Pharmaceuticals Inc.; Sanofi; and Takeda Pharmaceuticals.
- All other faculty and planners report no financial relationships relevant to this activity.

Understanding Multiple Myeloma, Its Treatment, and New Discoveries: Part 2

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Disclosures

- R. Donald Harvey, Pharm.D., FCCP, BCOP
  - Research funding (through Emory University): Acetylon Pharmaceuticals, Inc.; Bristol-Myers Squibb (BMS); Calithera Biosciences; Celgene Corporation; Cleave Biosciences; Novartis Pharmaceuticals; Onyx Pharmaceuticals Inc.; Sanofi; and Takeda Pharmaceuticals
  - Advisory boards: BMS, Onyx Pharmaceuticals Inc., and Takeda Pharmaceuticals
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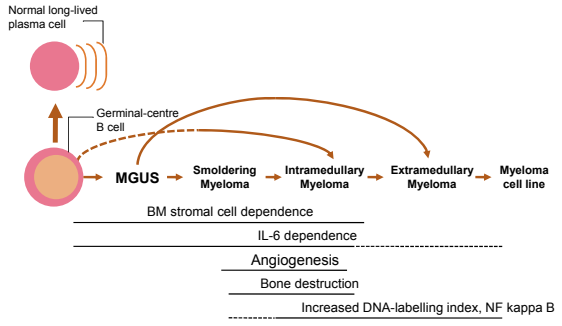
Learning Objectives

- Evaluate treatment regimens for patients with relapsed, refractory multiple myeloma
- Illustrate strategies for addressing the supportive care needs of patients with multiple myeloma who experience adverse reactions or develop complications
- Examine how current approaches to the treatment of multiple myeloma may evolve based on recent clinical trial data and new treatment discoveries

The First Webinar

- Background on clinical features of multiple myeloma
- Update on current therapies for initial treatment of multiple myeloma
- Tools to help develop an individualized therapeutic plan for patients from state-of-the-art clinical trial data

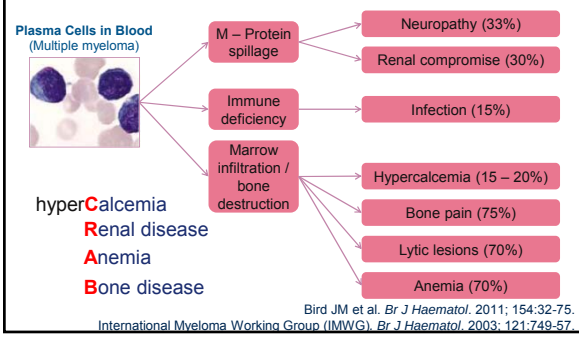
Plasma Cell Dyscrasias



Kuehl WM et al. *Nature Rev Cancer*. 2002; 2:175-87.

See enlargement p. 16

Signs and Symptoms of Myeloma



Bird JM et al. *Br J Haematol*. 2011; 154:32-75.
International Myeloma Working Group (IMWG). *Br J Haematol*. 2003; 121:749-57.

See enlargement p. 16

Myeloma Diagnostic Evaluation

- Medical history and physical examination
- Routine testing
  - CBC
  - Serum chemistries, including serum calcium
  - Serum and urine protein electrophoresis with immunofixation
  - Quantification of serum and urine monoclonal protein
  - Measurement of serum free light chains
- Bone marrow analysis
  - Trephine biopsy and aspirate of bone marrow cells for morphologic features; cytogenetic analysis and fluorescence in situ hybridization for chromosomal abnormalities
- Imaging
  - Skeletal survey, MRI if skeletal survey is negative

Kyle RA et al. *Leukemia*. 2009; 23:3-9.

Myeloma Diagnostic Criteria

- Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma and any one or more of the following myeloma defining events
- Myeloma defining events
  - Evidence of end-organ damage that can be specifically attributed to the underlying plasma cell proliferative disorder
  - Hypercalcemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
  - Renal insufficiency: creatinine clearance <40mL/min or serum creatinine >177 µmol/L (>2 mg/dL)
  - Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin level <100 g/L
  - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT or PET-CT

Rajkumar SV et al. *Lancet Oncol*. 2014;15:e538-e548.

Carfilzomib differs from bortezomib because

a. It can be given subcutaneously
b. Neuropathy is less common
c. Platelet counts are not affected
d. It does not increase risk for herpes infections

Patient Case Scenario

- FR is a 67-year-old patient with myeloma diagnosed in 2011, who received bortezomib and dexamethasone induction for 8 cycles followed by autologous stem cell transplant (SCT) with high-dose melphalan
- She presents with relapsed disease following SCT, and treatment with carfilzomib-lenalidomide-dexamethasone (CRd) is being considered

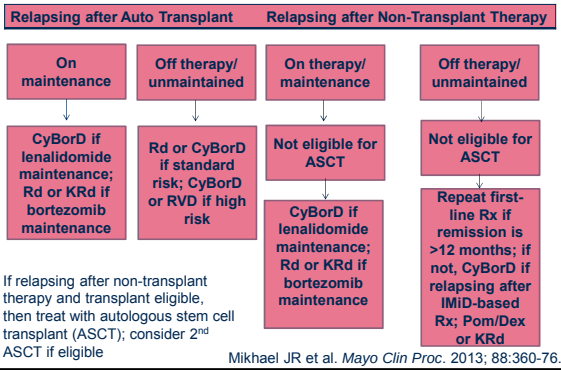
Which of the following considerations is important in FR for treatment selection with CRd?

a. Cardiac history
b. Bone disease
c. Neuropathy history
d. Mucositis with SCT

Considerations

- Single-agent versus combination therapies in relapsed/refractory disease
- Patient health may worsen with additional treatment and disease progression
  - Performance status
  - Comorbidities, treatment-emergent adverse events
- Combination trials of agents active in relapsed/refractory disease ongoing
  - Carfilzomib + pomalidomide

First Relapse



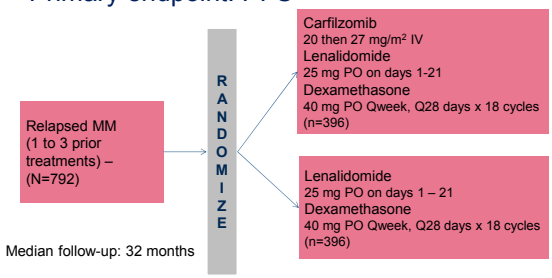
If relapsing after non-transplant therapy and transplant eligible, then treat with autologous stem cell transplant (ASCT); consider 2nd ASCT if eligible

Mikhael JR et al. *Mayo Clin Proc*. 2013; 88:360-76.

See enlargement p. 17

Carfilzomib-based Salvage Therapy

- Primary endpoint: PFS



Median follow-up: 32 months

Stewart AK et al. *N Engl J Med*. 2015; 372:142-52.

See enlargement p. 17

Efficacy

Parameter	Carfilzomib + Len + Dex	Len + Dex
PFS	26.3 months	17.6 months
OS at 24 months	73.3%	65%
RR	87.1%	66.7%
CR	31.8%	9.3%
Mean time to response	1.6 months	2.3 months
Median duration of response	28.6 months	21.2 months

PFS = progression free survival
OS = overall survival
RR = response rate
CR = complete response

Stewart AK et al. *N Engl J Med*. 2015; 372:142-52.

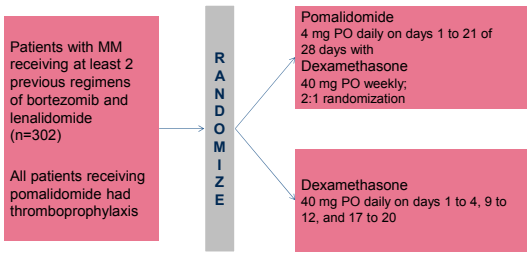
Toxicity

Parameter (≥ Grade 3)	Carfilzomib + Len + Dex	Len + Dex
Diarrhea	4%	4%
Fatigue	8%	6%
Pyrexia	2%	1%
Upper respiratory infection	2%	1%
Hypokalemia	9%	5%
Muscle spasms	1%	1%
Dyspnea	3%	2%
Hypertension	4%	2%
Acute renal failure	3%	3%
Cardiac failure	4%	2%
Ischemic heart disease	3%	2%

Stewart AK et al. *N Engl J Med*. 2015; 372:142-52.

Pomalidomide – Phase III Trial

- Primary endpoint: PFS



San Miguel J et al. *Lancet Oncol*. 2013; 14:1055-66.

See enlargement p. 18

Efficacy

Parameter	Pom + Dex (n=302)	Dex (n=153)
PFS	4.0 months	1.9 months
OS	12.7 months	8.1 months
TTP	4.7 months	2.1 months
ORR	31%	10%
CR/VGPR	6%	<1%

San Miguel J et al. *Lancet Oncol*. 2013; 14:1055-66.

Toxicity

Toxicity	Pom + Dex (n=302)	Dex (n=153)
Neutropenia	48%	16%
Anemia	33%	37%
Thrombocytopenia	22%	26%
Leukopenia	9%	3%
Febrile neutropenia	10%	0%
Pneumonia	13%	8%
Infection	30%	24%
Bone pain	7%	5%
Dyspnea	5%	5%

San Miguel J et al. *Lancet Oncol*. 2013; 14:1055-66.

Second or Later Relapse

Not Plasma Cell Leukemia (PCL) or Similar extramedullary disease (EMD)

Dual Refractory (bortezomib and lenalidomide)	Triple Refractory (bortezomib, lenalidomide, and carfilzomib)	Triple Refractory (bortezomib, lenalidomide, and pomalidomide)
KRd or Pom/dex to maximum response or 18 months, then Rd	PCD, PVD or Car-Pom-Dex to maximum response or 18 months, then Pom/Dex	KRd or Car-Pom-Dex to maximum response or 18 months, then Rd or Pom/Dex

- Auto transplant is an option, if transplant candidate and feasible
- Doublets such as cyclophosphamide-prednisone, pomalidomide-dexamethasone, and carfilzomib-dexamethasone could be considered in patients with indolent disease

Mikhael JR et al. *Mayo Clin Proc*. 2013; 88:360-76.

Second or Later Relapse

Secondary PCL or extensive EMD	Quadruple refractory (lenalidomide, pomalidomide, bortezomib and carfilzomib)
VDT-PACE x 2 cycles; Auto transplant if eligible; if not maintain with one of the regimens that the patient is not known to be refractory to	VDT-PACE x 2 cycles; Auto transplant if eligible; if not, consider alkylator-containing combination if not alkylator refractory or treat with anthracycline-containing regimen

- CVAD or similar regimen can be used in place of VDT-PACE in older patients or patients with poor functional status
- Other options to consider in fit patients: bendamustine or panobinostat-containing regimens.

Mikhael JR et al. *Mayo Clin Proc*. 2013; 88:360-76.

Adverse events attributable to panobinostat include

a. Fatigue, thrombocytopenia, diarrhea
b. Neuropathy, fever, dyspnea
c. Hypertension, neutropenia, rash
d. Thromboses, infections, hypocalcemia

Panobinostat Phase III Trial

- Primary end point: PFS

Relapsed Multiple Myeloma (1 to 3 prior treatments) – (N = 768)

RANDOMIZE

Panobinostat
20 mg PO days 1, 3, 5, 8, 10, 12;
Bortezomib
(1.3 mg/m^2) IV days 1, 4, 8, 11;
Dexamethasone
20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12;
Q21 days x 12 cycles

Bortezomib
(1.3 mg/m^2) IV days 1, 4, 8, 11;
Dexamethasone
20 mg PO on days 1, 2, 4, 5, 8, 9, 11, 12;
+ Placebo Q21 days x 12 cycles

Median follow-up 6 months

San Miguel J et al. *Lancet Oncol*. 2014; 15:1195-206.

See enlargement p. 18

Efficacy

Parameter	Panobinostat Arm (n = 387)	Control Arm (n = 381)
Median PFS	12 months	8 months
2-year PFS	20.6%	8.4%
Median OS	33.64 months	30.39 months
RR	60.7%	54.6%
CR	11%	6%
Near CR	17%	10%
Median time to response	1.51 months	2 months

San Miguel J et al. *Lancet Oncol*. 2014; 15:1195-206.

Toxicity – Grade III/IV

Parameter	Panobinostat Arm (n = 387)	Control Arm (n = 381)
Thrombocytopenia	68%	31%
Lymphopenia	54%	40%
Leukopenia	24%	8%
Neutropenia	35%	11%
Anemia	18%	19%
Diarrhea	25%	8%
Peripheral neuropathy	18%	15%
Asthenia/fatigue	24%	13%
Nausea	6%	2%
Vomiting	8%	1%
Pneumonia	13%	11%

San Miguel J et al. *Lancet Oncol*. 2014; 15:1195-206.

Panobinostat FDA Review

- FDA Oncologic Drug Advisory Committee recommended against approval in November 2014 because the group thought the benefits did not outweigh the toxicity risks
- Approval in February 2015 explicitly states that use is for patients with relapsed/refractory MM that have received at least 2 standard therapies including bortezomib and an IMiD agent
- FDA analyzed 193 patients in a prespecified subgroup of the Phase 3 trial that had received prior treatment with bortezomib and an IMiD agent
  - Median PFS: 10.6 months (n=94) panobinostat vs. 5.8 months (n=99) Control
  - RR: 59% panobinostat vs. 41% control

Food and Drug Administration.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435296.htm
(accessed 2015 Jul 27).

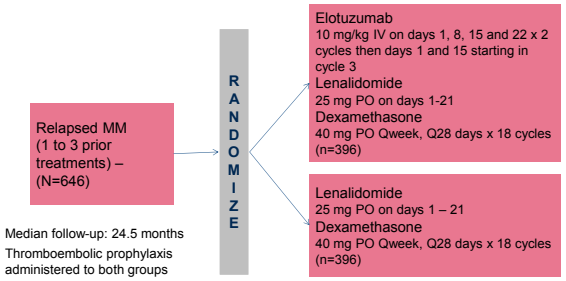
Panobinostat FDA Review

- Boxed warnings in package insert
  - Severe diarrhea
  - Cardiac events (including fatalities)
- Myelosuppression/bleeding/hepatotoxicity
- Risk evaluation and mitigation strategy program requirement
- FDA action taken under the accelerated approval program and the drug is designated as an orphan drug
- Further trials are required to confirm clinical benefit

Food and Drug Administration.
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm435296.htm
(accessed 2015 Jul 27).

Elotuzumab Phase III Trial

- Co-primary endpoints: PFS and Overall RR



Lonial S et al. *N Engl J Med*. 2015 Jun 2. [Epub ahead of print.]

See enlargement p. 19

Efficacy

Parameter	Elotuzumab (n=321)	Control (n=325)
PFS – 1 year	68%	57%
PFS – 2 year	41%	27%
Median PFS	19.4 months	14.9 months
Overall RR	79%	66%
CR	4%	7%
VGPR	28%	21%
PR	46%	38%
Minimal response/stable disease	16%	27%

Lonial S et al. *N Engl J Med*. 2015 Jun 2. [Epub ahead of print.]

Toxicity – Grade III/IV

Parameter	Elotuzumab (n=318)	Control (n=317)
Lymphocytopenia	77%	49%
Neutropenia	34%	44%
Anemia	19%	21%
Thrombocytopenia	19%	20%
Fatigue	8%	8%
Back pain	5%	4%
Diarrhea	5%	4%
Pyrexia	3%	3%
Insomnia	2%	3%
Peripheral edema	1%	1%
Constipation	1%	1%

Lonial S et al. *N Engl J Med*. 2015 Jun 2. [Epub ahead of print.]

Future Drug Targets in MM

Cell Surface Targets	Cytokines	BM Stroma	Adhesion Molecules
CD38	IL-6	NF-κB	ICAM-1
FGFR3	IGF-1	Smad	VCAM-1
SLAMF7 (CS1)	SDF-1α	ERK	Fibronectin
BAFF-R	BAFF	C-Myc	LFA-1
VEGFR	APRIL	PIM Kinase	MUC-1
	BSF-3		VLA-4

FGFR = fibroblast growth factor receptor; BAFF-R = B-cell activating receptor; VEGFR = vascular endothelial growth factor receptor; IL = interleukin; IGF = insulin-like growth factor; SDF = stroma cell-derived factor; APRIL = A Proliferation=inducing ligand; BSF = B-cell stimulating factor; NF-kB = nuclear factor kB; ICAM = intercellular adhesion molecule; VCAM = vascular cell adhesion molecule; LFA = lymphocyte function-associated antigen; MUC = mucin; VLA = very late antigen.

Anderson KC. *J Clin Oncol*. 2012; 30:445-52.

Selected Novel Agents

Oral proteasome inhibitors
- Ixazomib
- Oprozomib

Monoclonal antibodies
- Anti-SLAM7 (CS1), elotuzumab
- Anti-CD38
  - Daratumumab
  - SAR650984

Flianesib – kinesin spindle protein inhibitor

Developed alone and in combination strategies

Many in phase 3 trials

Patient Case Scenario

- FR receives her first 2 cycles of CRd (carfilzomib-lenalidomide-dexamethasone) without complications
- During her 3rd cycle, however, she is admitted for febrile neutropenia and develops renal insufficiency following IV contrast
- Her creatinine clearance is now 25 mL/min, down from 65 mL/min

How should CRd in FR be approached?

a. The regimen should be discontinued
b. Her carfilzomib should be reduced
c. Her lenalidomide should be reduced
d. No dose changes to the regimen

Supportive Care

The correct pairing of drug with adverse event is

a. Pomalidomide causes renal dysfunction
b. Carfilzomib causes thromboses
c. Bortezomib increases risk of cardiac dysfunction
d. Lenalidomide causes neutropenia

Toxicities and Complications

Drug	Toxicity	Management
Thalidomide, lenalidomide, pomalidomide	Venous thromboembolism (VTE)	Anticoagulation prophylaxis when combined with corticosteroids
Lenalidomide	Renal dysfunction (needs dose adjustment to prevent neutropenia and thrombocytopenia)	Adjust dose per prescribing information or avoid until renal function normalizes
Bortezomib	Peripheral neuropathy	Administer weekly, subcutaneous preferred over IV; carfilzomib has much lower rates of neuropathy
Bortezomib, Carfilzomib	Herpes zoster reactivation	Acyclovir or valacyclovir prophylaxis
Carfilzomib	Cardiac complications	Start at lower dose then titrate up
	Nephrotoxicity	Hydration
Corticosteroids	Hyperglycemia	Weekly corticosteroids preferred; sliding scale insulin and close monitoring in diabetic patients

See enlargement p. 19

Adjusting Therapy for End-Organ Dysfunction

Drug	Primary Route of Metabolism	Recommendations for Dosage Modification
Melphalan	Hydrolysis	Yes – reduce dose in hematopoietic SCT conditioning to 140 mg/m^2
Thalidomide	Renal	None
Lenalidomide	Renal	Adjust dose with CrCl <60 mL/min
Pomalidomide	Hepatic	None (ongoing study in renal dysfunction)
Bortezomib	Hepatic	Yes – reduce for elevated bilirubin
Carfilzomib	Peptidase cleavage and epoxide hydrolysis	None
Bisphosphonates	Renal	Yes – reduce for renal impairment

CrCl = creatinine clearance

See enlargement p. 20

Selected Dose Modifications

Bortezomib*	• Grade 4 hematologic, or grade ≥3 non-hematologic including neuropathy • 1.3 mg/m^2 → 1.0 mg/m^2 → 0.7 mg/m^2
Carfilzomib*	• Grade 3-4 hematologic, cardiac, pulmonary, hepatic, renal, neuropathy • 27 mg/m^2 → 20 mg/m^2 → 15 mg/m^2
Lenalidomide	• Any Grade 3-4 toxicity or platelet count ≤30K • 25 mg → 15 mg → 5 mg
Pomalidomide	• Grade 4 hematologic, or grade ≥3 non-hematologic • 4 mg → 3 mg → 1 mg

*Bortezomib and carfilzomib cause a unique thrombocytopenia that recovers quickly following dosing

See enlargement p. 20

Renal Dysfunction

- To avoid renal failure
  - Maintain hydration
  - Avoid use of NSAIDs
  - Avoid IV contrast
  - Plasmapheresis (NCCN category 2B)
- Renal dysfunction is not a contraindication to stem cell transplantation
- With chronic use of bisphosphonates, it is crucial to monitor for renal dysfunction

Renal Impairment (IMWG)

- Estimated GFR using modification of diet in renal disease equation
- Acute renal injury
  - RIFLE and Acute Renal Injury Network Criteria
- Rapid intervention to reverse renal damage
- Bortezomib-dexamethasone to rapidly reverse disease-induced nephropathy
- Lenalidomide may be used if dose adjusted for GFR
- Melphalan 140 mg/m^2 for CrCl <60 mL/min

GFR = glomerular filtration rate
RIFLE = risk, injury, failure, loss, and end-stage kidney disease
IMWG = International Myeloma Working Group

Dimopoulos MA et al. *J Clin Oncol*. 2010; 28:4976-84.

Skeletal Related Events

- Hypercalcemia of malignancy
- Pathologic fracture
- Bone pain
- Spinal cord compression
- Radiation therapy to the bone
- Bone surgery

Body JJ. *Support Care Cancer*. 2006;14:408-18.

Bone Disease (IMWG)

- Summary and comparison of existing guidelines (NCCN, ESMO, ASCO, Mayo, EMN)
- Compiled clinical trial data through August 2012
- Used level and grade of evidence convention to characterize recommendations
- Provide specific recommendation for bisphosphonates (BPs), surgery, and radiation

ESMO = European Society for Medical Oncology
ASCO = American Society of Clinical Oncology
EMN = European Myeloma Network

Terpos E et al. *J Clin Oncol*. 2013; 31:2347-57.

Bisphosphonate Recommendations

Patient Population	Recommendation
MM patients with detectable osteolytic lesions by conventional radiography receiving antimyeloma therapy	Pamidronate or zoledronic acid
Low-and intermediate-risk asymptomatic MM if osteoporosis documented	BP recommended
Osteoporosis in MGUS	BP recommended
Solitary lytic lesion and no evidence of osteoporosis	No BP therapy
Patients with solitary plasmacytoma	No BP therapy

Terpos E et al. *J Clin Oncol*. 2013; 31:2347-57.

Bisphosphonate Recommendations

- Pamidronate 30 and 90 mg have shown comparable efficacy in preventing skeletal-related events
  - IV is the preferred route of administration given at 3- to 4-week intervals
- Optimal duration for zoledronic acid is at least 2 years
- For patients not achieving CR or VGPR, pamidronate may be continued at prescriber discretion
- For patients in CR or VGPR, optimal duration ranges from 12 to 24 months
- Calcium and vitamin D3 supplementation should be used

Terpos E et al. *J Clin Oncol*. 2013; 31:2347-57.

Osteonecrosis of the Jaw

- Patients should be educated and receive a comprehensive dental examination
- Existing dental conditions should be treated before initiating BP therapy
- Following BP initiation, unnecessary dental procedures should be avoided with dental health evaluated annually
- Temporary suspension of BP therapy for 90 days before and after invasive dental work

Terpos E et al. *J Clin Oncol*. 2013; 31:2347-57.

Denosumab in Myeloma

- Treatment of myeloma bone involvement – not recommended
- Hypercalcemia and renal impairment
  - Denosumab pharmacokinetics not affected by renal impairment
  - Bisphosphonate refractory hypercalcemia
  - Risk of hypocalcemia
  - Optimal dosing: 120 mg vs. 60 mg vs. 3 mg/kg?

Henry DH et al. *J Clin Oncol*. 2011;29:1125-32.
Cicci JD et al. *Clin Lymphoma Myeloma Leuk*. 2014; 14:e207-11.
Hu MI et al. *J Clin Endocinol Metab*. 2014; 99:3144-52.

Peripheral Neuropathy: Duloxetine

231 cancer patients with at least grade 1 painful sensory neuropathy who were 25 years or older being treated at community and academic settings between April 2008 and March 2011

RANDOMIZE

- Duloxetine 30 mg PO daily x1 week then increase to 60 mg PO (two 30-mg capsules) daily
- Placebo 1 capsule PO daily x1 week then 2 capsules PO daily

Smith EM et al. *JAMA*. 2013; 309:1359-67.

Peripheral Neuropathy: Duloxetine

- Pain severity assessed using the Brief Pain Inventory-Short Form "average pain" 0-10 scale

Efficacy of Duloxetine			
	Duloxetine	**Placebo**	**P Value**
Mean Decrease in Pain	1.06 (95% CI, 0.72-1.40)	0.34 (95% CI, 0.01-0.66)	*P*=.003

- Other options: gabapentin, pregabalin, tricyclic antidepressants

Smith EM et al. *JAMA.* 2013; 309:1359-67.

Herpes Zoster Prophylaxis with Proteasome Inhibitors

- Immunocompromised patients at risk of developing varicella zoster virus (VZV) infection
- Bortezomib and carfilzomib are associated with increased risk of VZV infection
- Acyclovir and other antiviral prophylaxis appear effective at preventing VZV infection (with or without corticosteroids)
- Vaccine not recommended

Vickrey E et al. *Cancer.* 2009; 115:229-32.

Optimal thromboprophylaxis in patients without cardiac history treated with immunomodulators is

a. Full-dose rivaroxaban
b. Mini-dose warfarin
c. Low-dose aspirin
d. Full-dose low molecular weight heparin (LMWH)

Baseline Risk for VTE

Parameter	VTE Rate
MGUS	6.1%
MM	3 – 10%
Dexamethasone induction	3 – 4%
Thalidomide-dexamethasone (high-dose) induction	14 – 26%
Lenalidomide-dexamethasone (high-dose) induction	26%
Lenalidomide-dexamethasone (low-dose) induction	12%

Srkalovic G et al. *Cancer.* 2004; 101:558-66.
Sallah S et al. *Ann Oncol.* 2004; 15:1490-4.
Rajkumar SV et al. *J Clin Oncol.* 2006; 24:431-6.
Rajkumar SV et al. *Lancet Oncol.* 2010; 11:29-37.

Prophylaxis Strategies

Treatment Arm	VTE Rate During First 6-Month Observation	Cumulative Proportion of VTE Events at 12 Months	Major Bleeding
Aspirin 100 mg/day (n=176)	2.27%	2.3%	0
Low molecular weight heparin 40 mg/day (n=166)	1.2%	1.8%	0
P value	0.452	NR	NA

Larocca A et al. *Blood.* 2012; 119:933-9.

Prophylaxis for Thalidomide-Dexamethasone

Parameters	Aspirin (100 mg/day) (n=220)	Warfarin (1.25 mg/day) (n=220)	LMWH (40 mg/day) (n=219)
Composite primary endpoint – 6 months	6.4%	8.2%	5%
Composite primary endpoint – 24.9 months	8.6%	10%	7.8%
Major bleeding	1.4%	0	0

Primary endpoint was a composite measure of patients developing a first episode of objectively confirmed symptomatic DVT, PE, arterial thrombosis, any acute cardiovascular event (acute myocardial infarction or stroke) or sudden, otherwise unexplained death (presumed to be a result of PE, acute myocardial infarction or stroke) during the first 6 months from random assignment.

Palumbo A et al. *J Clin Oncol.* 2011; 29:986-93.

Conclusion

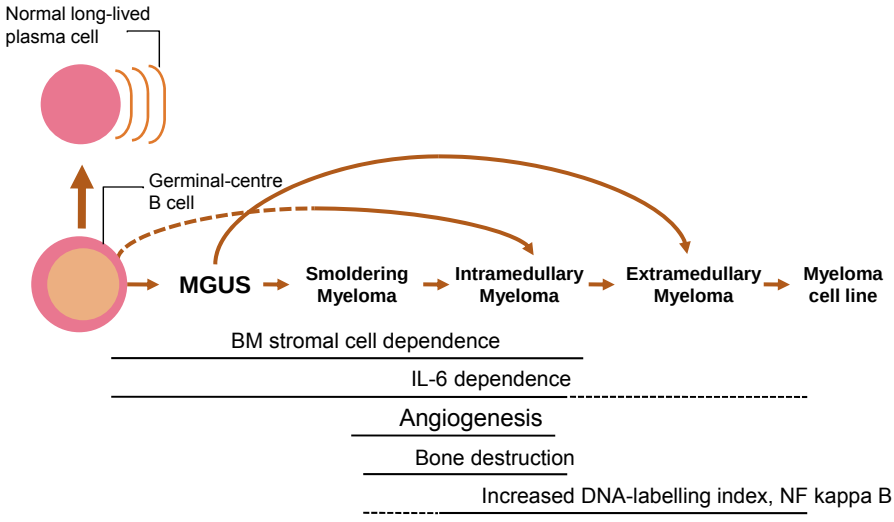
- Patients with relapsed/refractory multiple myeloma should have treatment selected based on prior therapies and goals of treatment
- Adverse events of these treatments may be specific to agent class (e.g., thrombotic events) or more broad (e.g., cytopenias) and should be assessed prior to beginning treatment
- Investigational agents with novel targets will continue to improve patient outcomes

Key References

- Nooka AK, Kastritis E, Dimopoulos MA, Lonial S. Treatment options for relapsed and refractory multiple myeloma. *Blood*. 2015; 125:3085-99.
- Varga C, Laubach J, Hideshima T et al. Novel targeted agents in the treatment of multiple myeloma. *Hematol Oncol Clin North Am*. 2014; 28:903-25.
- Raje NS, Yee AJ, Roodman GD. Advances in supportive care for multiple myeloma. *J Natl Compr Canc Netw*. 2014; 12:502-11.

Questions?

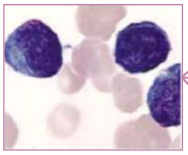
Plasma Cell Dyscrasias



Kuehl WM et al. *Nature Rev Cancer*. 2002; 2:175-87.

Signs and Symptoms of Myeloma

Plasma Cells in Blood
(Multiple myeloma)



M – Protein spillage
- Neuropathy (33%)
- Renal compromise (30%)

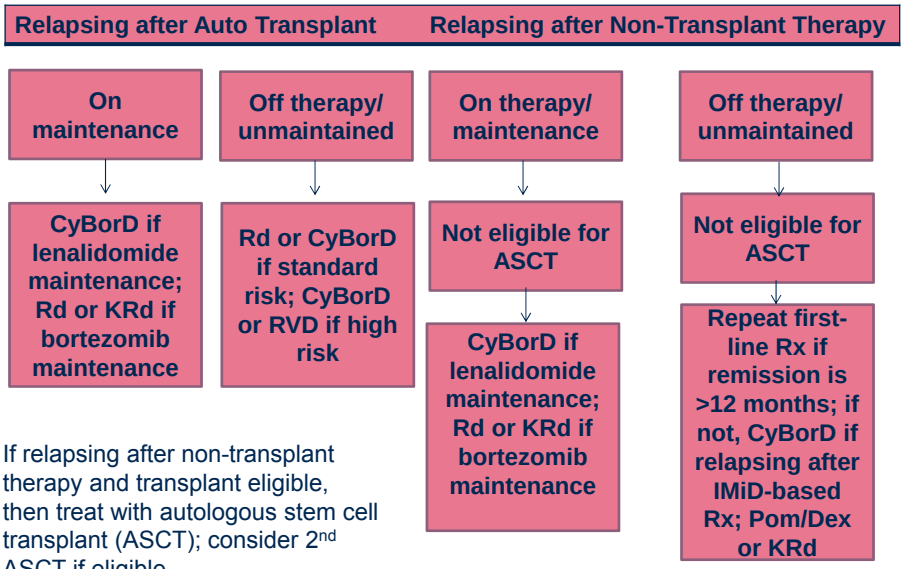
Immune deficiency
- Infection (15%)

Marrow infiltration / bone destruction
- Hypercalcemia (15 – 20%)
- Bone pain (75%)
- Lytic lesions (70%)
- Anemia (70%)

hyper**C**alcemia
Renal disease
Anemia
Bone disease

Bird JM et al. *Br J Haematol*. 2011; 154:32-75.
International Myeloma Working Group (IMWG). *Br J Haematol*. 2003; 121:749-57.

First Relapse

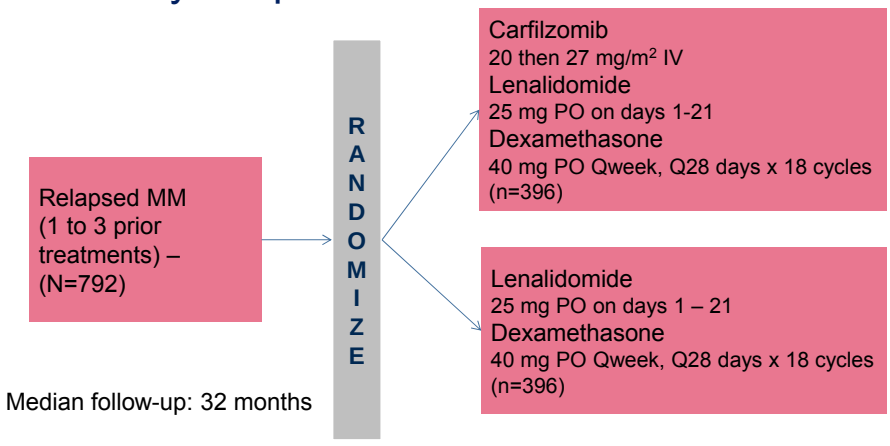


If relapsing after non-transplant therapy and transplant eligible, then treat with autologous stem cell transplant (ASCT); consider 2nd ASCT if eligible

Mikhael JR et al. *Mayo Clin Proc*. 2013; 88:360-76.

Carfilzomib-based Salvage Therapy

- Primary endpoint: PFS

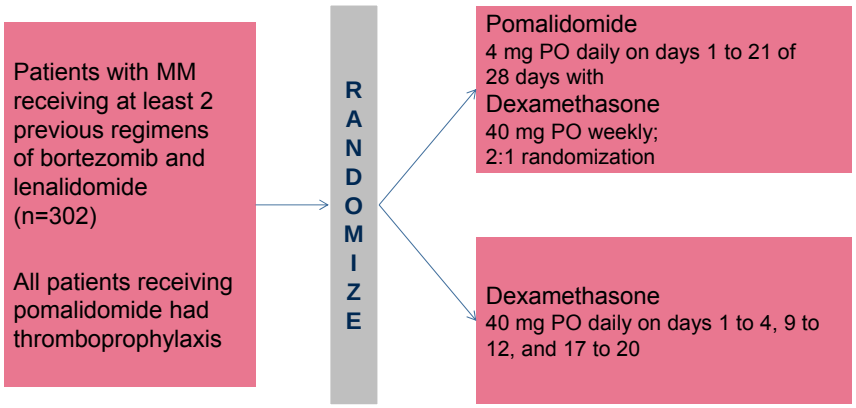


Median follow-up: 32 months

Stewart AK et al. *N Engl J Med*. 2015; 372:142-52.

Pomalidomide – Phase III Trial

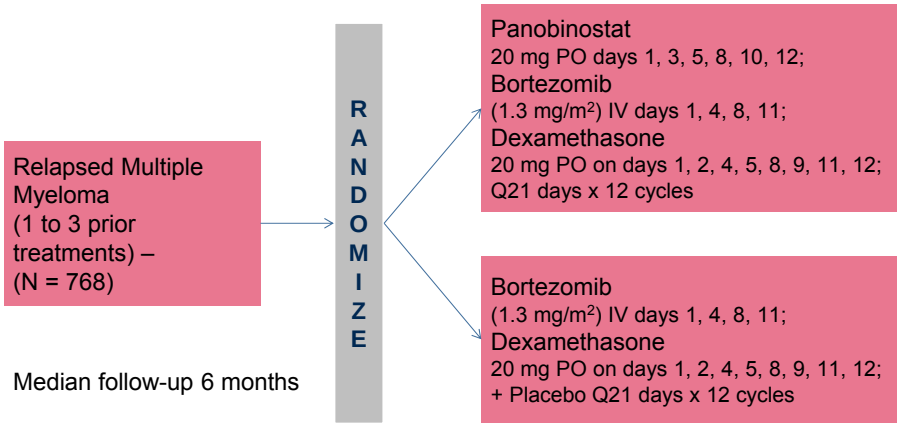
- Primary endpoint: PFS



San Miguel J et al. *Lancet Oncol*. 2013; 14:1055-66.

Panobinostat Phase III Trial

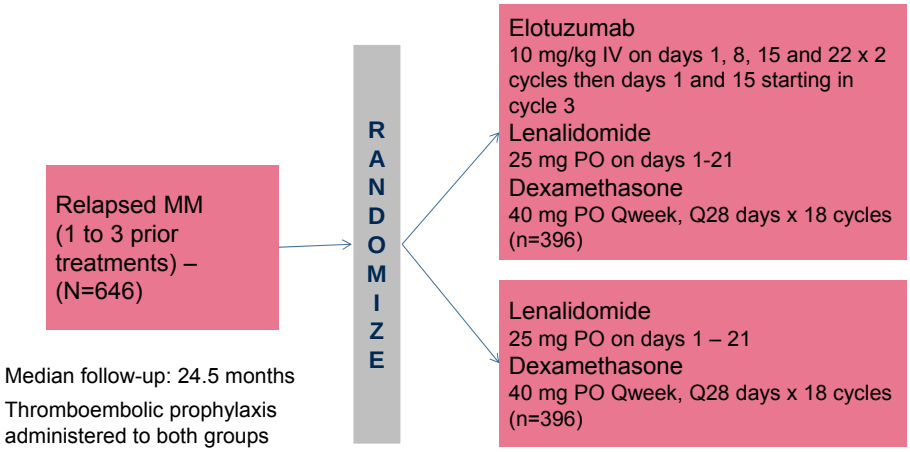
- Primary end point: PFS



San Miguel J et al. *Lancet Oncol*. 2014; 15:1195-206.

Elotuzumab Phase III Trial

- Co-primary endpoints: PFS and Overall RR



Median follow-up: 24.5 months

Thromboembolic prophylaxis administered to both groups

Lonial S et al. *N Engl J Med*. 2015 Jun 2. [Epub ahead of print.]

Toxicities and Complications

Drug	Toxicity	Management
Thalidomide, lenalidomide, pomalidomide	Venous thromboembolism (VTE)	Anticoagulation prophylaxis when combined with corticosteroids
Lenalidomide	Renal dysfunction (needs dose adjustment to prevent neutropenia and thrombocytopenia)	Adjust dose per prescribing information or avoid until renal function normalizes
Bortezomib	Peripheral neuropathy	Administer weekly, subcutaneous preferred over IV; carfilzomib has much lower rates of neuropathy
Bortezomib, Carfilzomib	Herpes zoster reactivation	Acyclovir or valacyclovir prophylaxis
Carfilzomib	Cardiac complications	Start at lower dose then titrate up
	Nephrotoxicity	Hydration
Corticosteroids	Hyperglycemia	Weekly corticosteroids preferred; sliding scale insulin and close monitoring in diabetic patients

Adjusting Therapy for End-Organ Dysfunction

Drug	Primary Route of Metabolism	Recommendations for Dosage Modification
Melphalan	Hydrolysis	Yes – reduce dose in hematopoietic SCT conditioning to 140 mg/m^2
Thalidomide	Renal	None
Lenalidomide	Renal	Adjust dose with CrCl <60 mL/min
Pomalidomide	Hepatic	None (ongoing study in renal dysfunction)
Bortezomib	Hepatic	Yes – reduce for elevated bilirubin
Carfilzomib	Peptidase cleavage and epoxide hydrolysis	None
Bisphosphonates	Renal	Yes – reduce for renal impairment

CrCl = creatinine clearance

Selected Dose Modifications

Bortezomib*
- Grade 4 hematologic, or grade ≥3 non-hematologic including neuropathy
- 1.3 mg/m^2 → 1.0 mg/m^2 → 0.7 mg/m^2

Carfilzomib*
- Grade 3-4 hematologic, cardiac, pulmonary, hepatic, renal, neuropathy
- 27 mg/m^2 → 20 mg/m^2 → 15 mg/m^2

Lenalidomide
- Any Grade 3-4 toxicity or platelet count ≤30K
- 25 mg → 15 mg → 5 mg

Pomalidomide
- Grade 4 hematologic, or grade ≥3 non-hematologic
- 4 mg → 3 mg → 1 mg

*Bortezomib and carfilzomib cause a unique thrombocytopenia that recovers quickly following dosing

Self-assessment Questions

These questions will be discussed during the activity. Record the answers here for your future reference.

1. Carfilzomib differs from bortezomib because
    a. It can be given subcutaneously
    b. Neuropathy is less common
    c. Platelet counts are not affected
    d. It does not increase risk for herpes infections

Questions 2 and 4 refer to the following patient case scenario.

FR is a 67-year-old patient with myeloma diagnosed in 2011, who received bortezomib and dexamethasone induction for 8 cycles followed by autologous stem cell transplant (SCT) with high-dose melphalan. She presents with relapsed disease following SCT, and treatment with carfilzomib-lenalidomide-dexamethasone (CRd) is being considered.

2. Which of the following considerations is important in FR for treatment selection with CRd?
    a. Cardiac history
    b. Bone disease
    c. Neuropathy history
    d. Mucositis with SCT

3. Adverse events attributable to panobinostat include
    a. Fatigue, thrombocytopenia, diarrhea
    b. Neuropathy, fever, dyspnea
    c. Hypertension, neutropenia, rash
    d. Thromboses, infections, hypocalcemia

4. FR receives her first 2 cycles of CRd (carfilzomib-lenalidomide-dexamethasone) without complications. During her third cycle, however, she is admitted for febrile neutropenia and develops renal insufficiency following IV contrast. Her creatinine clearance is now 25 mL/min, down from 65 mL/min. How should CRd in FR be approached?
    a. The regimen should be discontinued
    b. Her carfilzomib should be reduced
    c. Her lenalidomide should be reduced
    d. No dose changes to the regimen

5. The correct pairing of drug with adverse event is
    a. Pomalidomide causes renal dysfunction
    b. Carfilzomib causes thromboses
    c. Bortezomib increases risk of cardiac dysfunction
    d. Lenalidomide causes neutropenia

6. Optimal thromboprophylaxis in patients without cardiac history treated with immunomodulators is
    a. Full-dose rivaroxaban
    b. Mini-dose warfarin
    c. Low-dose aspirin
    d. Full-dose low molecular weight heparin (LMWH)

List of Abbreviations Used in Presentation

APRIL	a proliferation-inducing ligand
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
BAFF-R	B-cell activating receptor
BM	bone marrow
BP	bisphosphonate
BSF	B-cell stimulating factor
CBC	complete blood count
CI	confidence interval
CR	complete response
CRAB	hyperCalcemia, Renal disease, Anemia, Bone disease
CrCl	creatinine clearance
CRd	carfilzomib-lenalidomide-dexamethasone
CT	computed tomography
CVAD	cyclophosphamide-vincristine-doxorubicin-dexamethasone
CyBorD	cyclophosphamide-bortezomib-dexamethasone
EMD	similar extramedullary disease
EMN	European Myeloma Network
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FGFR	fibroblast growth factor receptor
GFR	glomerular filtration rate
ICAM	intercellular adhesion molecule
IGF	insulin-like growth factor
IL	interleukin
IMiD	immunomodulatory drug
IMWG	International Myeloma Working Group
IV	intravenous
KRd	carfilzomib-lenalidomide-dexamethasone
LFA	lymphocyte function-associated antigen
LMWH	low molecular weight heparin
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRI	magnetic resonance imaging

MUC	mucin
NCCN	National Comprehensive Cancer Network
NF-kB	nuclear factor kB
NSAIDs	nonsteroidal anti-inflammatory drugs
ORR	overall response rate
OS	overall survival
PCD	pomalidomide-carfilzomib-dexamethasone
PCL	plasma cell leukemia
PET	positron emission tomography
PFS	progression free survival
PO	by mouth
PR	partial response
PVD	pomalidomide-bortezomib-dexamethasone
Rd	lenalidomide-dexamethasone
RIFLE	risk, injury, failure, loss, and end-stage kidney disease
RR	response rate
RVD	bortezomib-lenalidomide-dexamethasone.
SCT	stem cell transplant
SDF	stroma cell-derived factor
TTP	time to progression
VCAM	vascular cell adhesion molecule
VDT-PACE	bortezomib-dexamethasone-thalidomide-cisplatin-doxorubicin-cyclophosphamide-etoposide
VEGFR	vascular endothelial growth factor receptor
VGPR	very good partial response
VLA	very late antigen
VZV	varicella-zoster virus