Clinical Updates & Issues: Relapsed/Refractory Multiple Myeloma

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National Comprehensive Cancer Network®

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Learning Objectives

- Identify advances in systemic treatment of relapsed/refractory multiple myeloma.
- Describe the complexities in treating relapsed/refractory multiple myeloma.
- Recognize and manage adverse events associated with therapies used to treat relapsed/refractory multiple myeloma.

Treating Myeloma is Not Easy….

- **Accurate diagnosis is required**
- **Attention to Relapse, emerging data**
- **Goals of treatment:**
  - Rapid and effective control of disease
  - Manage disease-related symptoms
  - Improve survival
  - Maintain quality of life while on therapy

Drug and disease-related adverse events may interfere with one's ability to remain on therapy

Kumar S. *Curr Hematol Malig Rep*. 2011;6(2):104-12.

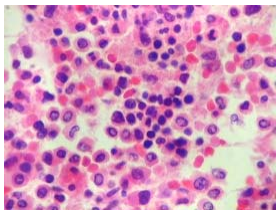
Challenges of Effective Treatment

- **Patient**
  - Comorbid conditions
  - Trust in the provider (Impacts adherence)
- **Polypharmacy**
  - Confusion
  - Disease sequelae
- **Healthcare**
  - Access to effective drugs
  - Communication
  - Identify and intervene adverse events (AEs)

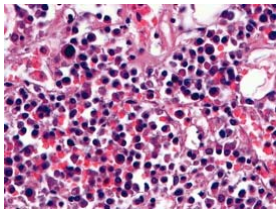
Nurses are critical in the identification and intervention of AEs, keeping patients on therapy

Myeloma Is a Cancer of Plasma Cells

normal bone marrow



myeloma bone marrow

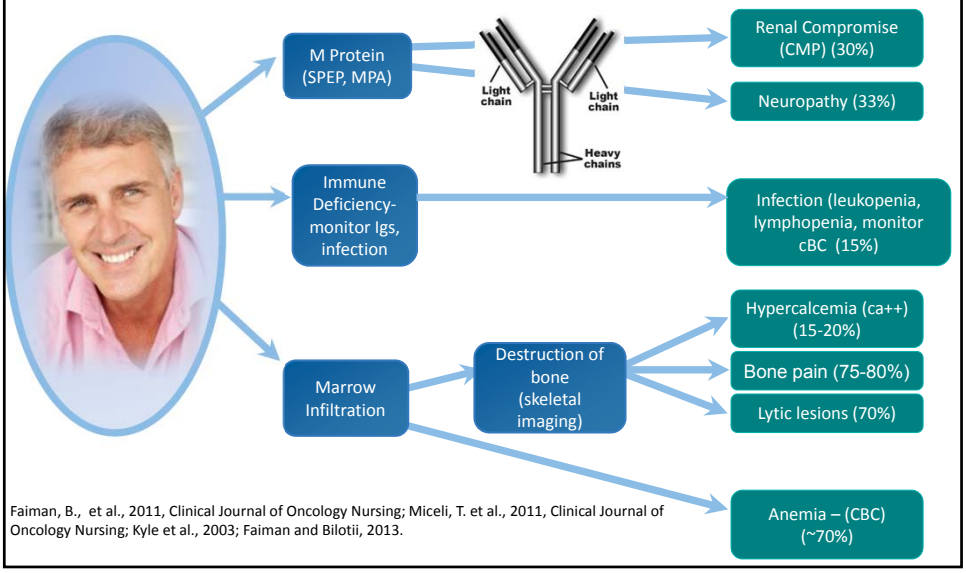


- Cancer of plasma cells
- Often preceded by nonmalignant state(s): MGUS or SMM
- Healthy plasma cells produce antibodies/immunoglobulins (Ig)
- Overproduction of a normal Ig "clone"
  - 65% IgG
  - 20% IgA
  - Baseline and ongoing monitoring of the disease is essential: CBC, CMP, SPEP, UPEP, serum free light chains

MGUS = monoclonal gammopathy of undetermined significance; SMM = smoldering multiple myeloma SPEP= serum protein electrophoresis UPEP= Urine protein electrophoresis CBC= complete blood count CMP Complete metabolic panel

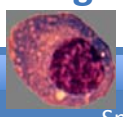
Kyle RA, et al. *Mayo Clin Proc.* 2003;78:21-33; Cross TS, et al. *Postgrad Med J.* 2006;82:e13-e13.

The Multiple Effects of Multiple Myeloma

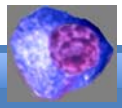


Faiman, B., et al., 2011, Clinical Journal of Oncology Nursing; Miceli, T. et al., 2011, Clinical Journal of Oncology Nursing; Kyle et al., 2003; Faiman and Bilotii, 2013.

Criteria for Diagnosis of Myeloma: CRAB



Pre-Malignant — *More Genetic Damage* — **Malignant**



MGUS	Smoldering MM	**Symptomatic MM**
o < 3 g/dL M spike	o ≥ 3 g/dL M spike	o Increased PC ≥ 10%
o < 10% PC	o AND/OR ≥ 10% PC	o Any M spike +

AND → NO

AND one or more of the following:

- o **C**alcium ↑ in serum (> 11.5 mg/dL)
- o **R**enal insufficiency (SCr > 2 mg/dL)
- o **A**nemia (Hgb < 10 g/dL or 2g below nl)
- o **B**one lesions or osteoporosis
- o Abnormal SFLC ratio >100
- o MRI >1 focal lesion
- o BMBX plasma cell >60%

MGUS = monoclonal gammopathy of undetermined significance; PC = plasma cells in bone marrow; SCr = serum creatinine; Hgb = hemoglobin

NCCN Guidelines for Multiple Myeloma v.3.2016; Kyle et al, 2010; Durie et al, 2006; Rajkumar SV, et al. *Lancet Oncology.* 2014; 15:e538-e548. Kyle RA, et al. *Leukemia.* 2010; 24:1121–1127.

Treatment Options Have Greatly Increased – US

Side effect identification and management is critical to keep patients "fit" for the next therapy

1960 1970 1980 1990 2000 2010

Approved relapsed indications for 2015/2016:

- Ixazomib + lenalidomide + dexamethasone, >1 prior therapy
- Daratumumab monotherapy ≥3 prior therapies
- Elotuzumab + lenalidomide + dexamethasone, >prior therapy
- Carfilzomib + lenalidomide + dexamethasone, >1-3 prior therapy
- Carfilzomib 20/56mg/m2 IV

FDA-Approved in MM

2008 1st line Bortezomib

2012 Bortezomib SC

Dex= Dexamethasone SC - subcutaneous

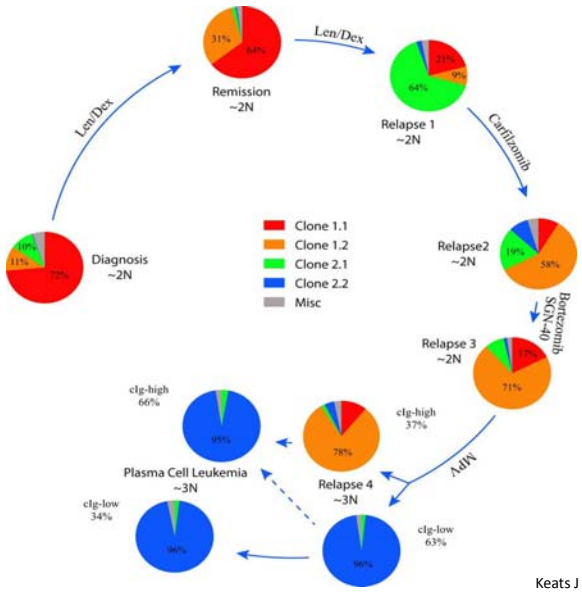
DRUGS@FDA.gov

New drugs, new studies, new indications: 2015

Drug(s)	Study Population	Implications
Daratumumab Single agent and in combination with len/dex , pom /dex	RRMM	Newly approved MOAB; infusion reaction, toxicities
"TOURMALINE MM" Ixazomib + len/dex + Pan/dex + Ctx/dex	NDMM/RRMM	All oral combinations; adherence, cost
"ELOQUENT-2" + len/dex	RRMM	Infusion – related
"ASPIRE"- CaRd vs Rd Car/Pom/dex; Car/Pan/dex	RRMM	Timing of Carfilzomib; cardiac
Bortezomib - SWOG 0777 - RVDlite	NDMM	3 vs 2 drugs upfront

Moreau et al. Abstract 727; Reu et al. Abstract 4221; Kumar et al. Abstract 3050; Shah et al. Abstract 3155; Usmani et al. Abstract 29; Kumar et al. Abstract 3050; Avet-Loiseau et al. Abstract 731; Palumbo et al. Abstract 510; Sonneveld et al. Abstract 27; Dimopoulos et al. Abstract 28; Chng et al. Abstract 30; Durie et al. Abstract 25; O'Donnell et al. Abstract 4217

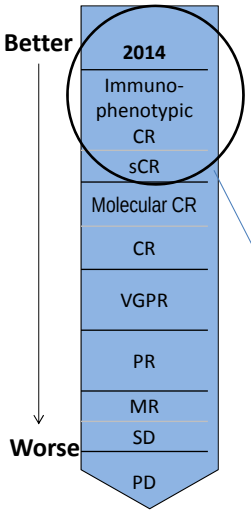
Multiple Myeloma Is a Clonal Disease; However, the Clones Change Over Time



- Effective treatment reduces or eliminates the dominant clone
- Other clones can still exist.
- On-going treatment to suppress clones

Keats J J et al. *Blood* 2012;120:1067-1076.

Monitoring Disease is Essential: IMWG Myeloma Response Criteria



Category	Response Criteria
sCR, stringent complete response	Normal free light chain (FLC); no clonal BM plasma cells
CR, complete response	Negative IFX and < 5% BM plasma cells
VGPR, very good partial response	Positive IFX and negative SPEP; ≥ 90% urine protein decrease; urine M-protein level < 100 mg per 24 h
PR, partial response	≥ 50% decrease serum M-protein and ≥ 90% decrease in 24 h urinary M-protein
SD, stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease

- sCR AND BM negative by next gen flow (10^6)
- CR AND normal FLC ratio, BM negative by flow, 2 measures
- CR AND negative PCR (10^5)
- CR: Negative immunofix; <5% PC in BM; 2 measures

sCR= Stringent Complete Response; CR = Complete Response; VGPR = Very Good Partial Respnse; PR = Partial Response; SD = Stable Disease; MR = Minimal Response (only in relapsed); PD = Progressive Disease

Palumbo A, et al. International Myeloma Working Group. *J Clin Oncol.* 2014; 32:587-600. Durie BM, et al; International Myeloma Working Group. *Leukemia.* 2006; 20(9):14671473.

Select Preferred Regimens from the NCCN Guidelines for MM

- **NCCN Category 1**
  - Bortezomib
    - SC vs IV administration
  - Bortezomib/PLD
  - Carfilzomib/lenalidomide/dexamethasone
  - Panobinostat/bortezomib/dexamethasone
  - Lenalidomide/dexamethasone
  - Ixazomib/len/dex
  - Elotumab/len/dex
- **NCCN Category 2A**
  - Repeat primary induction therapy if relapse at > 6 mos
  - Daratumumab
  - Bortezomib combinations
    - With dex; len/dex; thalidomide
  - Carfilzomib
  - Cyclophosphamide
    - High-dose or with bort/dex or len/dex
  - Pomalidomide/dexamethasone
  - Thalidomide/dexamethasone
  - DCEP, DT-PACE, or VTD-PACE

NCCN Guidelines for Multiple Myeloma: v.3.2016.

Factors in Selecting Treatment for Relapsed/Refractory Myeloma

- Disease-related factors
  - Duration of response to initial therapy
  - High/low risk status
  - Biochemical disease progression, or symptomatic?
  - Other comorbid conditions
- Treatment-related factors
  - Previous therapy exposure (relapsed or refractory)
  - Toxicity of regimen (combination vs single agent)
  - Mode of administration (eg, oral or IV)
  - Cost and convenience (out of pocket copays for IV/Oral)

Strategies at Relapse: Start low, go slow.. or "Go for it"?

Treating Indolent, Slow-Growing Myeloma in First Relapse	Treating Relapsed/Refractory Myeloma	Aggressive Myeloma With Rapid, Multiple Relapses
• If initial treatment with bortezomib, len repeat or change therapy • Ixazomib, carfilzomib and elotuzumab are all considerations with len/dex • Consider if high/low risk disease at diagnosis	▪ Any peripheral neuropathy or renal dysfunction? ▪ What has been tried (PI-based, IMId- based ▪ Are clinical trials available?	▪ Transplant if not done (allo, auto) ▪ Chemotherapy – based salvage with aggressive clones is often necessary ▪ MoAb candidates

****Remember to discuss goals and costs of therapy at each stage**
Encourage health maintenance to maintain "fitness" for next therapy

Proper Dosing of Drugs Can Minimize AEs

***Geriatric assessment- Risk Factors:**

- Age over 75 years
- Mild, moderate, or severe frailty (weakness, poor endurance, weight loss, low physical activity, and slow gait speed)
- Comorbidities: cardiac, pulmonary, hepatic, or renal dysfunction

Drug	Dosing Based on Risk Factors* Including Age		
	No risk factors	At least 1 risk factor Adjusted Dose	At least 1 risk factor plus occurrence of GR 3-4 non-hematological AE
Bortezomib	1.3 mg/m^2 biweekly d 1,4,8,11 /3 wks	1.3 mg/m^2 weekly d 1,8,15,22 /5 wks	1.0 mg/m^2 weekly d 1,8,15,22 /5 wks
Lenalidomide	25 mg/d d 1-21 of 28-day cycle	15 mg/d d 1-21 of 28-day cycle	10 mg/d d 1-21 of 28-day cycle
Dexamethasone	40 mg weekly d 1,8,15,22 /4 wks	20 mg weekly d 1,8,15,22 /4 wks	10 mg weekly d 1,8,15,22 /4 wks
Melphalan	0.25 mg/kg or 9 mg/m^2 d 1-4 / 4-6 wks	0.18 mg/kg or 7.5 mg/m^2 d 1-4 / 4-6 wks	0.13 mg/kg or 5 mg/m^2 d 1-4 / 4-6 wks
Thalidomide	100 mg per day	50 mg per day	50 mg qod

Pmbo et al., Blood, 2015; alumbo A, et al. *Blood*. 2011;118:4519-4529.

Lenalidomide

- Class: IMiD (thalidomide analogue)
- FDA approval: 2006
- Administration: oral
- Dose: 25 mg once daily orally on Days 1-21 of q 28-day
- Dose adjust for renal insufficiency

Indication

- Multiple myeloma, in combination with dexamethasone for NDMM, RRMM
- In combination with Elo, Ixa, Carfilzomib

Adverse Events

Most common (≥20%):

- **Fatigue**, neutropenia, constipation, diarrhea, muscle cramp, anemia, pyrexia, peripheral edema, nausea, back pain, upper respiratory tract infection, dyspnea, dizziness, thrombocytopenia, tremor and rash

**Educate and evaluate:

- REMS: Embryo-fetal toxicity
- Hematologic toxicity – neutropenia and thrombocytopenia
- Venous thromboembolism – DVT and PE

IMiD = immunomodulatory drug; REMS = Risk Evaluation and Mitigation Strategy; DVT = deep vein thrombosis; PE = pulmonary embolism.
Lenalidomide® Prescribing Information, 2013.

Bortezomib

- Class: proteasome inhibitor
- FDA approval: 2003
- Administration: subcutaneous or intravenous
- Dose: recommended starting dose is 1.3 mg/m^2
  - Administered intravenously at a concentration of 1 mg/mL as a 3 to 5 second bolus IV injection
  - Administered subcutaneously at a concentration of 2.5 mg/mL

Indication

- Treatment of patients with multiple myeloma

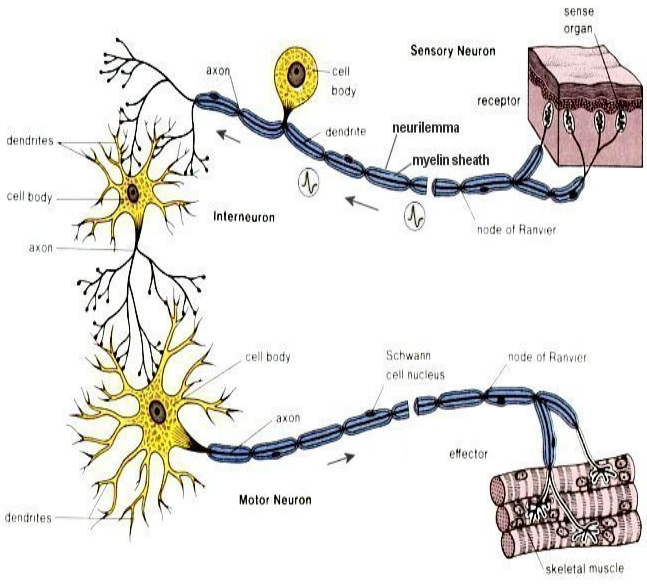
Most Commonly Reported Adverse Reactions (incidence ≥ 20%) in Clinical Studies

- **Nausea**, diarrhea, **thrombocytopenia**, neutropenia, **peripheral neuropathy**, fatigue, neuralgia, anaemia, leukopenia, constipation, vomiting, lymphopenia, rash, pyrexia, and anorexia.

Mateos, MV, et al. ASH 2013 #1968.
Bortezomib® Prescribing Information, 2015; .

Possible Side Effect of Treatment: Peripheral Neuropathy (PN)

- Sensory, motor, autonomic
- Risk
- Symptoms
- Side effect of MM treatment or the disease



Cavaletti et al., 2007; Smith et al., 2013

Peripheral Neuropathy (PN): Risk Factors and General Considerations

Non-MM Causes of PN:

- Endocrine disorders
  - Hypothyroidism
  - Diabetes
- Nutritional disease
  - Vitamin B deficiency
  - ETOH
- Connective tissue disease
- Vascular disease
- Medications
- Herpes zoster
- Most common symptoms
  - Sensory deficits, pain

MM Disease- and Treatment-Related

Hyperviscosity syndrome

- Hypergammaglobulinemia
- Incidence of PN in untreated pts: 39%
- Incidence of grade 3/4 PN
  - Bortezomib: 26% to 44%
    - ↓ with weekly vs twice weekly dosing
    - ↓ with SC administration
  - Thalidomide: 28% to 41%
    - ↑ with higher doses duration
    - Carfilzomib: overall 14%
  - Pomalidomide: Mild, up to 9%

Richardson et al., 2012; Gleason C, et al. J Natl Compr Cancer Netw. 2009;7:971-979. Palumbo A, et al. J Clin Oncol. 2014;32:587-600. Kurtin S, et al. J Adv Pract Oncol. 2013;4:307-321: Pomalidomide prescribing, 2015.

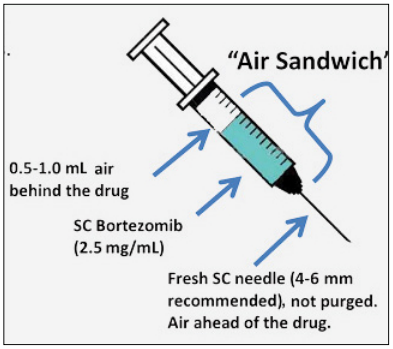
Minimize PN with Bortezomib SC

Peripheral Neuropathy

- Major reason for dose reduction, discontinuation
- SC and weekly can minimize risk of PN

Subcutaneous (SC)

- FDA approved SC in 2012
- Equivalent efficacy as IV
- Reduced neuropathy and GI AEs with SC
- **Skin / Infection site reactions**
- Reconstitution



For subcutaneous administration
Add 1.4 mL
0.9% sodium chloride

Two ways to reconstitute a 3.5-mg vial of bortezomib

For intravenous administration
Add 3.5 mL
0.9% sodium chloride

Shah, et al. ASH 2012 #2968; Barbee, et al. ASCO 2012 #E18553; Moreau P, et al. ASH 2011 #1863; Moreau P, et al. *Lancet Oncol.* 2011;12(5):431; Bortezomib prescribing information.

Peripheral Neuropathy (PN) Management

- Prevention / management:
  - Once-weekly or SC administration of bortezomib
  - Dose reduce thalidomide or other agent (mild PN is associated with pomalidomide, carfilzomib)
  - Ensure no other causes of PN (check b vitamins, glucose)
  - Recommend exercise, massage to stimulate blood flow
  - Safe environment: rugs, furnishings, shoes, driving
- Pharmacologic:
  - Supplements are generally safe: B-complex vitamins (B1, B6, B12), folic acid, and/or amino acids but do not take on day of bortezomib infusion
  - L glutamine, b vitamins, alpa-lipoic acid,
  - Duloxetine (30-60 mg/day) , gabapentin, pregabalin
  - Opioid analgesic agents
- Mild:
  - Consider holding, dose reduction or discontinuation of offending agent
- If moderate to severe:
  - **Stop the drug**

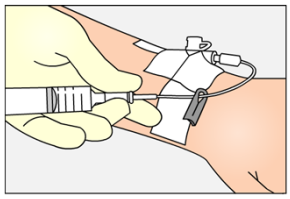
Tariman, et al. *Clin J Oncol Nurs*. 2008;12(3 Suppl):29-36.

Carfilzomib: IV Administration 2 Days per Week

Carfilzomib: Approved for RRMM in the US at Two Dose levels:

1) 20/27mg/m2 with len/dex, or
2) 20/56 mg/m2 monotherapy

- ASPIRE: 792 patients randomly assigned to carfilzmib/len/dex or len/dex; median PFS 26.3months, vs. 17.6 months
- ENDEAVOR: 929 pts randomly assigned to carfilzomib/dex or bortezomib/dex median PFS 18.7 months, vs. 9.4 months
- Pre-medicate and hydrate
  - Antiemetic and fluids before carfilzomib C1
  - After (optional)
- Administer carfilzomib IV
  - **over 30minutes**
  - Rinse IV with saline before & after
- Monitor: may require dose adjustment for toxicities
- DVT risk



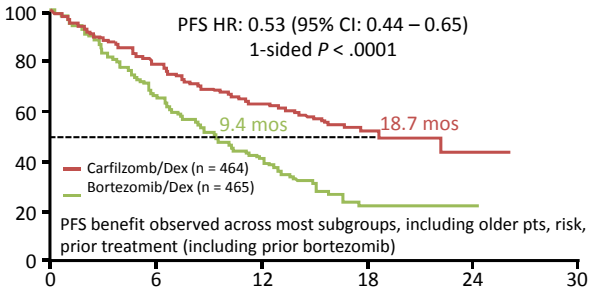
Carfilzomib 28-day Cycle						
1	**2**	3	4	5	6	7
8	**9**	10	11	12	13	14
15	**16**	17	18	19	20	21
22	23	24	25	26	27	28

Cycle 1, week 1: **20** mg/m^2
Cycle 1, week 2+: **27 or 56**mg/m^2

Source: Amgen, 2016. Carfilzomib prescribing information

ENDEAVOR: Carfilzomib/dex results in 2-fold increase in median PFS vs bortezomib/dex in relapsed MM

- *Pts with symptomatic RR MM after 1-3 prior treatments with ≥ PR to ≥ 1 prior regimen (N = 792)*
- Significant PFS improvement and higher response rates with carfilzomib/dex vs bortezomib/dex in relapsed MM; ORR: 77% vs 63% (*P* < .0001), respectively



- Rates of d/c to due AEs similar (14% vs 16%), but rates of grade ≥ 3 hypertension (25% vs 9%), dyspnea (5% vs 2%), and heart failure (5% vs 2%) increased with carfilzomib vs bortezomib; rates of grade ≥ 2 peripheral neuropathy increased with bortezomib/Dex vs carfilzomib/dex (32% vs 6%)

Dimopoulos MA, et al. 2016

Phase III ASPIRE: Len/Dexamethasone ± Carfilzomib in RR MM

- Randomized, open-label, multicenter phase III trial

Stratified by β_2-microglobulin, prior bortezomib, and prior lenalidomide

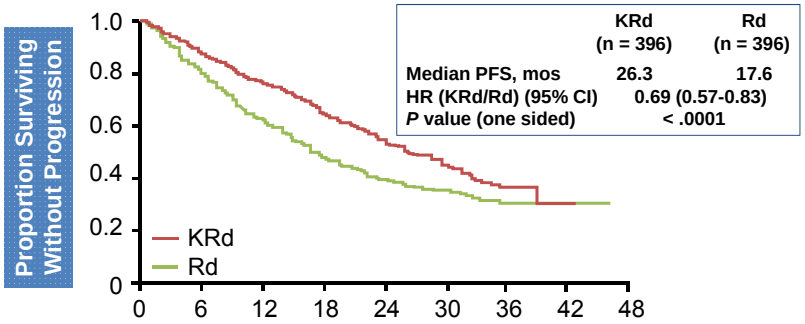
Pts with symptomatic RR MM after 1-3 prior treatments with ≥ PR to ≥ 1 prior regimen (N = 792)

KRd
Carfilzomib* 27 mg/m^2 IV Days 1, 2, 8, 9, 15, 16 (20 mg/m^2 Days 1, 2, cycle 1 only) +
Lenalidomide 25 mg Days 1-21 +
Dexamethasone 40 mg Days 1, 8, 15, 22
(n = 396)

Rd
Lenalidomide 25 mg Days 1-21 +
Dexamethasone 40 mg Days 1, 8, 15, 22
(n = 396)

Stewart AK, et al. N Engl J Med. 2015;372:142-152.

Len/Dexamethasone ± Carfilzomib in RR MM (ASPIRE): PFS (ITT)



Risk Group by FISH	KRd (n = 396)		Rd (n = 396)		HR	P Value
	n	Median PFS, Mos	n	Median PFS, Mos		
High	48	23.1	52	13.9	0.70	.083
Standard	147	29.6	170	19.5	0.66	.004

Stewart AK, et al. N Engl J Med. 2015;372:142-152.

ASPIRE: Select Adverse Events

Select Adverse Events	KRd (n = 392)	Rd (n = 389)
	All Grades, %	All Grades, %
Nonhematologic AEs occurring in ≥25% of pts		
▪ Diarrhea	42.3	33.7
▪ Fatigue	32.9	30.6
▪ Cough	28.8	17.2
▪ Pyrexia	28.6	20.8
▪ Upper respiratory tract infection	28.6	19.3
▪ Hypokalemia	27.6	13.4
▪ Muscle spasms	26.5	21.1
Hematologic AEs occurring in ≥ 25% of pts		
▪ Anemia	42.6	39.8
▪ Neutropenia	37.8	33.7
▪ Thrombocytopenia	29.1	22.6
Other AEs of Interest		
▪ Dyspnea	19.4	14.9
▪ Peripheral neuropathy	17.1	17.0
▪ Hypertension	14.3	6.9
▪ Acute renal failure	8.4	7.2
▪ Cardiac failure	6.4	4.1
▪ Ischemic heart disease	5.9	4.6

Implications

Monitor blood counts

Monitor for infection

Cardiac

- EKG for patients with cardiac history, ECHO baseline
- **Diuretics, inhalers, minimize fluids, longer infusion time (30 mins)**

Advise patient on

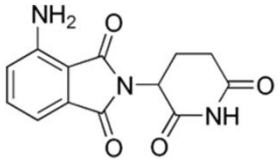
- Shortness of breath (dyspnea)
- Fatigue
- Cytopenias
- Infection prevention
- VTE prophylaxis

Source: Amgen, 2016. Carfilzomib prescribing information
Stewart AK, et al. N Engl J Med. 2015;372:142-152

Pomalidomide

Pomalidomide

- Class: IMiD
- Indication: patients with MM
  - Have received at least 2 prior therapies
  - PD within 60 days of last therapy
- FDA Approval: February 8, 2013
- Administration: Oral
- Metabolism/Clearance
  - Liver via CYP1A2 and CYP3A4
- Can be ± low-dose dex
- REMS Program



- Pomalidomide prolongs survival
- Pomalidomide has a manageable safety profile with few discontinuations due to AE's
- Pomalidomide maintains quality of life and provides oral convenience for patients

Pomalidomide Prescribing Information Highlights.

Pomalidomide Implications: Administration

Implications:

- Anti-thrombotic treatment
- Embryonic/fetal toxicity
  - Child-bearing age female
    - Two negative pregnancy tests
    - Abstinence or 2 forms birth control
  - Male: drug present in semen
    - Latex or synthetic condom with females of reproductive potential
- Pomalidomide REMS™ Program

Discuss Administration With Patient:

- 4 mg once daily on days 1-21 of 28-day cycle
- Available in strengths: 1, 2, 3 or 4 mg capsules
- Take without food
  - At least 2 hrs before or after a meal
- Do not break, chew, or open the capsules
- Adherence: consistent schedule (AM or PM)
  - Take immediately if <12 hours since missed dose
  - Skip and take next regular dose if >12 hours

Pomalidomide prescribing information highlights.

Pomalidomide Implications: AEs & Patient Management

Pomalidomide Grade 3/4 AEs in >10%	
Adverse Event	Percent
Neutropenia	47
Anemia	22
Thrombocytopenia	22
Pneumonia	16
Fatigue & asthenia	11
Back pain	12

Pomalidomide Common AEs (in >30%)	
Adverse Event	Percent
Fatigue and asthenia	55
Neutropenia	52
Constipation	38
Nausea	36
Diarrhea	34
Dyspnea	34
Upper resp. tract infection	32
Back pain	32
Pyrexia (pom+dex)	30

Implications

- DVT prophylaxis
- Monitor blood counts
- Monitor for neuropathy although less common

Educate patients on

- DVT prophylaxis
- Infection risk / blood counts
- Fatigue
- REMS

Source: Pomalidomide Prescribing Information Highlights

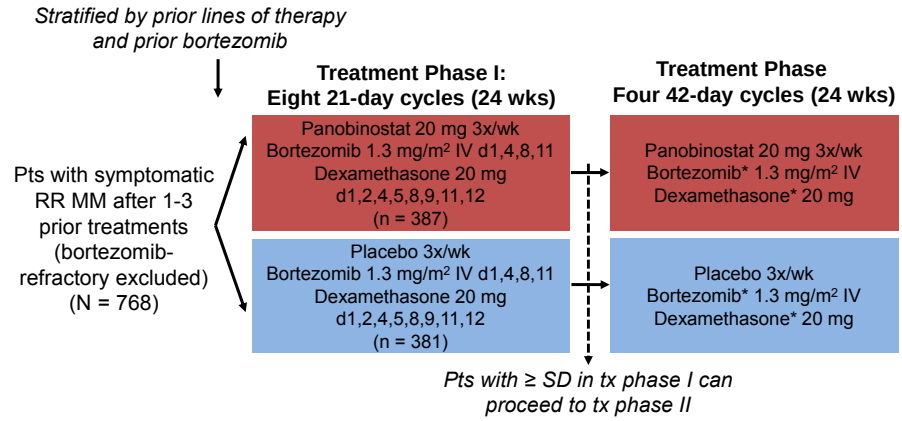
Newly approved drugs and indications- 2015

	Panobinostat	Ixazomib	Daratumumab	Elotuzumab
Indication	FDA approved in 2015 combination with bortezomib and dexamethasone, in patients who have received ≥ 2 prior regimens, including bortezomib and an immunomodulatory agent	FDA approved on 11/20/15 [len + dex] ± ixazomib in adult patients with relapsed/refractory multiple myeloma who have received 1-3 prior therapies	FDA approved on 11/16/15 in patients with ≥ 3 prior lines of therapy, including both a proteasome inhibitor and an immunomodulatory agent, or who are refractory to a proteasome inhibitor and an immunomodulatory agent	FDA approved on 11/30/15 [len + dex] ± elotuzumab in adult patients with relapsed/refractory multiple myeloma who have received 1-3 prior therapies
Administration	20 mg, taken orally once every other day for 3 doses per week (on Days 1, 3, 5, 8, 10, and 12) of Weeks 1 and 2 of each 21-day cycle for 8 cycles	4 mg taken orally on Days 1, 8, 15	16 mg/kg IV on Days 1, 8, 15, and 22 of cycles 1 and 2 (weekly dosing), on Days 1 and 15 of cycles 3 to 6 (every 2 weeks dosing), and on Day 1 of cycle 7 and subsequent cycles (every 4 weeks dosing)	10 mg/kg IV, weekly, on Days 1, 8, 15, 22 (cycles 1 & 2); Days 1 and 15 (cycles 3 and beyond)

FDA.gov; prescribing information

Phase III PANORAMA 1: Bort/Dex ± Panobinostat in RR Myeloma

- Randomized, double-blind trial
- Primary endpoint reached: median PFS ↑ by 3.9 mos



San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206.

Panobinostat + bortezomib, dexamethasone

PANOBINOSTAT (Oral) – CYCLES 1-8 (28-Day Cycles)														
	Week 1							Week 2						
	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7
Panobinostat	✓		✓		✓			✓		✓		✓		
Bortezomib	✓			✓				✓			✓			

PANOBINOSTAT (Oral) – CYCLES 9-16 (28-Day Cycles)														
	Week 1							Week 2						
	D 1	D 2	D 3	D 4	D 5	D 6	D 7	D 1	D 2	D 3	D 4	D 5	D 6	D 7
Panobinostat	✓		✓		✓			✓		✓		✓		
Bortezomib	✓							✓						
Dexamethasone	✓	✓						✓	✓					

Panobinostat. PI. 2015.

PANORAMA 1: Safety and implications

	Select AEs (≥ 10% Incidence and ≥ 5% Greater Incidence With Pan), %	Pan + Bort/Dex (n = 381)		Pbo + Bort/Dex (n = 377)	
		All Grades	Grade 3/4	All Grades	Grade 3/4
Cardiac, GI and Heme toxicity	Arrhythmia	12	3	5	2
	Diarrhea	68	25	42	8
	Nausea	36	6	21	1
	Vomiting	26	7	13	1
	Fatigue	60	25	42	12
	Peripheral edema	29	2	19	<1
	Thrombocytopenia	97	67	83	31
	Anemia	62	18	52	19
	Neutropenia	75	34	36	11
	Leukopenia	81	23	48	8
	Lymphopenia	82	53	74	40

Evaluate and treat diarrhea, fatigue, watch for myelosuppression
Peripheral neuropathy with bortezomib

Richardson P, et al. ASCO 2014. Abstract 8510^. San-Miguel JF, et al. Lancet Oncol. 2014;15:1195-1206.

Tourmaline RRMM: Ixazomib + len/dex vs len/dex

- 722 patients randomized 1:1 to receive ixazomib 4 mg or matching placebo weekly on d 1, 8, and 15, plus lenalidomide 25 mg PO on d 1-21 and dexamethasone 40 mg PO on d 1, 8, 15, and 22, in 28-d cycles
  - Many high-risk patients and prior exposure to btz; study favored IRd to Rd in early relapse MM

	IRd	Rd	HR / OR
Median PFS, mos	20.6	14.7	HR 0.742; 95% CI: 0.587-0.939; P = 0.012
Confirmed ORR, %	78.3	71.5	OR 1.44; P = 0.035
CR	11.7	6.6	OR 1.87; P = 0.019
≥ VGPR	48.1	39.0	OR 1.45; P = 0.014
Median time to first response (ITT analysis), mos	1.1	1.9	
Median duration of response (≥ PR), mos	20.5	15.0	

Moreau et al. Abstract 727. Moreau et al. *Blood*.2014;124(7):986-987.

Phase III TOURMALINE-MM1: IRD vs RD in Relapsed and/or Refractory MM

System Organ Class, n(%)	IRd, N=360			Rd, N=360		
	All	Grade 3	Grade 4	All	Grade 3	Grade 4
Upper respiratory tract infection	69 (19)	1 (<1)	0	52 (14)	2 (<1)	0
Peripheral neuropathies	**100 (28)**	**7 (2)**	**0**	**77 (21)**	**7 (2)**	0
Diarrhea	151 (42)	22 (6)	0	130 (36)	8 (2)	0
Constipation	122 (34)	1 (<1)	0	90 (25)	1 (<1)	0
Nausea	92 (26)	6 (2)	0	74 (21)	0	0
Vomiting	79 (22)	4 (1)	0	38 (11)	2 (<1)	0
Rash	**68 (19)**	**9 (3)**	**0**	**38 (11)**	**5 (1)**	**0**
Back pain	74 (21)	2 (<1)	0	57 (16)	9 (3)	0
Edema, peripheral	91 (25)	8 (2)	0	66 (18)	4 (1)	0

Ixazomib: An oral proteosome inhibitor, three times monthly dosing

IXAZOMIB (Oral) – 28-DAY CYCLES								
	Week 1		Week 2		Week 3		Week 4	
	D 1	D 2-7	D 8	D 9-14	D 15	D 16-21	D 22	D 23-28
Ixazomib	✓		✓		✓			
Lenalidomide	✓	✓ QD	✓	✓QD	✓	✓QD		
Dexamethasone	✓		✓		✓		✓	

- Implications:
- Dose reduce for hepatic impairment
- Nausea, rash and thrombocytopenia can occur
- HSV prophylaxis
- Rapidly absorbed

Ixazomib. PI. 2015.

ELOQUENT-2: Results and Safety

- Pts with relapsed/refractory MM and 1-3 prior therapies (N = 646), randomized to elo+ Rd or Rd
- Significant PFS improvement and higher response rates with elotuzumab + RD vs RD alone in relapsed MM
  - ORR: 79% vs 66% (*P* = .0002), respectively
- Infusion reactions reported in 10% of pts (9% grade 1/2; 1% grade 3); 70% occurred with initial dose; 2 discontinuations (1%) due to infusion reaction

Selected Grade 3/4 AEs, %	Elo-Ld (n = 318)	Ld (n = 317)
Lymphopenia	77	49
Neutropenia	34	44
Infection	28*	24*
Nonhematologic in > 1% of pts ▪ Fatigue ▪ Diarrhea ▪ Pyrexia	 9 5 3	 8 4 3

*Incidence similar after controlling for duration of therapy.

Elotuzumab: Dose and Schedule

Implications:
- Infusion reaction prevention
- HSV prophylaxis
- DVT prophylaxis (lenalidomide)

ELOTUZUMAB (IV) – CYCLES 1 AND 2 (28-Day Cycles)

	Week 1		Week 2		Week 3		Week 4	
	D 1	D 2-7	D 8	D 9-14	D 15	D 16-21	D 22	D 23-28
Elotuzumab	✓		✓		✓		✓	
Lenalidomide	✓	✓ QD	✓	QD	✓	QD		
Dexamethasone	✓		✓		✓		✓	

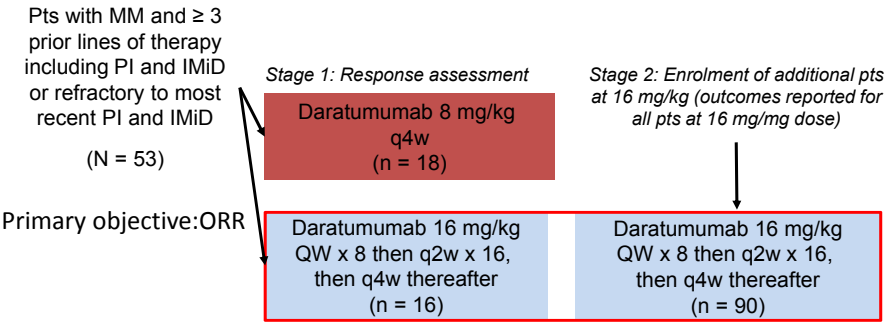
ELOTUZUMAB (IV) – CYCLES 3 AND BEYOND (28-Day Cycles)

	Week 1		Week 2		Week 3		Week 4	
	D 1	D 2-7	D 8	D 9-14	D 15	D 16-21	D 22	D 23-28
Elotuzumab	✓				✓			
Lenalidomide	✓	✓ QD	✓	QD	✓	QD		
Dexamethasone	✓		✓		✓		✓	

Prescribing information, 2015

Phase II SIRIUS: Daratumumab Monotherapy in Heavily Pretreated RR MM

- Open-label, international, multicenter, 2-stage study



- Primary objective:ORR
  - Median PFS: 3.7 mos (95% CI: 2.8-4.6); 1-yr OS: 65% (95% CI: 51.2-75.%)
  - Most common grade 3/4 AEs: thrombocytopenia (25%), anemia (24%), neutropenia (14%); infusion-related reactions occurred in 43% (most grade 1/2)

Lonial S, et al. ASCO 2015. Abstract LBA8512.

Daratumumab

DARATUMUMAB (IV) – WEEKS 1-8

	Week 1		Week 2		Week 3		Week 4	
	D 1	D 2-7	D 8	D 9-14	D 15	D 16-21	D 22	D 23-28
Daratumumab	✓		✓		✓		✓	

DARATUMUMAB (IV) – WEEKS 9-24

	Week 1		Week 2		Week 3		Week 4	
	D 1	D 2-7	D 8	D 9-14	D 15	D 16-21	D 22	D 23-28
Daratumumab	✓				✓			

DARATUMUMAB (IV) – WEEKS 25 +

	Week 1		Week 2		Week 3		Week 4	
	D 1	D 2-7	D 8	D 9-14	D 15	D 16-21	D 22	D 23-28
Daratumumab							✓	

- Must pre-post medicate with hydrocortisone
- Moneleukast and loratadine 10mg each the night before and for 48 hrs after infusion
- Type/cross match and antibody workup necessary

- Daratumumab-related sAEs:
- Pneumonia, neutropenia, diarrhea (1 pt each receiving 16 mg/kg, early infusion program);
- Laryngeal edema (1 pt receiving 16 mg/kg, accelerated infusion program)
- 19 of 45 pts reported infusion-related reactions; mostly grade 1/2

Daratumumab. PI. 2015.

Additional Agents Currently in Development

Agent	MOA	Phase in Development
Ibrutinib	Tyrosine kinase inhibitor (BTK, ERK1/2, others)	I and II
Filanesib	Kinesin spindle protein (KSP) inhibitor	II
Indatuximab ravtansine	CD138 antibody-drug conjugate	I and II
Ricolinostat	HDAC inhibitor	I and I/II
Selinexor (KPT-330)	XPO_1 nuclear transport inhibitor	I and II
MOR202 (MOR03087)	anti-CD38 antibody	I/II
Venetoclax (ABT-199/GDC-0199)	Selective BCL-2 inhibitor	I
Oprozomib	Proteosome inhibitor, oral	III
SAR650984	Anti CD38 antibody	I/II

Clinicaltrials.gov

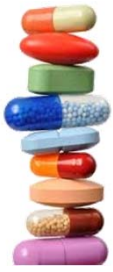
Adherence to treatment must be addressed

- Cancer should be a reason to take medications
- Can be intentional and non- intentional
- Reasons why people don't take their pills or office visits :

  "I feel fine", "I forgot", "I cant remember all these pills!",
  "I don't need them anymore", "can't afford treatments"

•Discuss reasons for non- adherence (intentional, non-intentional) and employ strategies to improve adherence

  •Telephone reminders, alarms, calendars, help from significant others



Faiman, B. (2011). Journal of Advanced Practitioner in Oncology, 2 26-34; Accrodino and Hershman (2013). Am Soc. Clin. Oncol. Educ. Book. 2013;2013:271-6. doi: E10.1200/EdBook_AM. 2013.33.271. PubMed PMID: 23714520

Other considerations to manage side effects: Myelosuppression and Infection

- Myelosuppression is associated with both myeloma and the drugs used to treat it; treat MM if disease related
  - Risk of infection increased due to hypogammaglobulinemia
  - Dose-modifications, growth factors for neutropenia
  - Mild leukopenia, anemia and thrombocytopenia can be treatment related
- Infection prophylaxis
  - Pts should remain up to date on appropriate vaccinations (influenza, pneumonia)
  - HSV prophylaxis when receiving Pis, MOAbs
  - Use of IVIG or prophylactic antibiotics is controversial and should only be used when warranted
  - Pt education emphasizing importance of alerting treating clinicians of potential infection can reduce unnecessary antibiotics

Faiman, B. and Bilotti, E. (2013) Chapter 10: Multiple Myeloma. In: Olsen, M., and Zitella, L. (Eds). *Hematologic Malignancies.* Pittsburgh: ONS Publishing Division. Pp. 445-498.

Gastrointestinal (GI)

- Constipation, nausea, and diarrhea can occur
- GI symptoms are generally mild
- Nausea
  - Make sure the patient is on PPI
  - Assess for other competing meds that may cause
- Constipation
  - Bowel regimen
- Diarrhea
  - Rule out cdiff or other infection, investigate other causes, imodium or lomotil

Smith et al. IMF Nurse Leadership Board. *Clin J Oncol Nurs*. 2008;12(3 Suppl):53-63.

Treatment Side Effect: Steroids

- Side effects affect every body system
  - AM v PM dosing
  - Take with food
  - Mood stabilizers
  - Monitor for hyperglycemia

Faiman B, Bilotti E, Mangan PA, Rogers K; IMF Nurse Leadership Board. *Clin J Oncol Nurs*. 2008;12(3 Suppl):53-63.

Venous Thromboembolic Events: Signs and Symptoms of clot in MM

DVT

- Slight fever
- Rapid heart rate
- Unilateral swelling, erythema, warm extremity
- Cyanosis/cool skin if blockage
- Dull ache, pain, tight feeling over area and palpation
- Homan's sign (35% patients)

PE

- Anxiety
- Sudden shortness of breath
- Chest discomfort
- Rapid pulse and heart rate
- Low-grade fever
- Pleural friction rub, crackles, diminished breath sounds, wheezing

Rome et al. *CJON*. 2008;*12*(3, Suppl.):21–27.

Risk Assessment for VTEs in Pts Receiving Imids or carfilzomib

- **MM is an inherently coagulable state and risk can change over time**
- VTE prophylaxis for individual risk factors (eg, age or obesity) or myeloma-related risk factors (eg, immobilization or hyperviscosity)
  - If ≤ 1 risk factor present, aspirin 81-325 mg/day
  - If ≥ 2 risk factors present, LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin (target INR: 2-3)
  - Higher incidence VTEs with carfilzomib
- VTE prophylaxis for myeloma therapy–related risk factors (eg, high-dose dexamethasone, IMiDs, doxorubicin, multiagent chemotherapy)
  - LMWH (equivalent to enoxaparin 40 mg/day) or full-dose warfarin (target INR: 2-3)
  - Direct acting oral anticoagulants?

LMWH = low molecular weigt heparin.
Rome, S et al., 2008; Palumbo A, et al J Clin Oncol. 2014;32:587-60; Palumbo, A;(2008). Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia, 22*(2), 414-423.; Faiman, and Bilotti, 2014; Amgen, 2016

Current Management of Bone Disease

- Treat the myeloma
- Novel therapies have benefits
  - Direct effect on inflammatory cytokines
  - Inhibition of bone resorption
  - Osteoclast stimulation
- Bisphosphonates
  - Pamidronate
  - Zoledronic acid
- Supplement with calcium and vitamin D3 to maintain calcium homeostasis
- Radiotherapy (low dose)
  - Impending fracture
  - Cord compression
  - Plasmacytomas
- Vertebroplasty/kyphoplasty
- Orthopedic consultation
  - Impending or actual long-bone fractures
  - Bony compression of spinal cord
  - Vertebral column instability

Routine dental visits, watch for osteonecrosis of the jaw, a rare but serious complication

Niesvizky R, et al. J Natl Compr Canc Netw. 2010;8(suppl 1):S13-S20. Christoulas D, et al. Expert Rev Hematol. 2009;2:385-398. Drake MT. Oncology (Williston Park). 2009;23(14 suppl 5):28-32. Terpos E, et al. J Clin Oncol. 2013;31:2347-2357. Webb SL, et al. Br J Pharmacol. 2014;[Epub ahead of print].

Survivorship in MM: Key Points

- Survivorship begins at diagnosis
- Patients are living longer than ever
- Health maintenance practices are highly important
- Adherence to therapies are critical to maintain remission, remain healthy for next therapy
- Prevention of infection, falls
- Care of the caregivers

Bilotti E, Gleason C, McNeill A, the International Myeloma Foundation Nurse Leadership B. Routine Health Maintenance in Patients Living With Multiple Myeloma. *Clinical journal of oncology nursing. 2011;15(0):25-40.*

Table 1 Adverse events commonly associated with multiple myeloma therapeutic agents

		PN	*Myopathy*	*VTE*	*Thrombocytopenia*	*Neutropenia*	*Lymphopenia*	*Anemia*	*Decreased NK cells*	*Infection*	*Pneumonia*	*Fatigue*	*Nausea*	*Diarrhea*	*Constipation*	*2° primary malignancy*	*High blood glucose*	*Infusion reaction*	*Osteoporosis*	*Rash*	*Edema*	*Mood disorders*
PIs	Bortezomib	X			X					X		X	X	X	X							
	Carfilzomib				X	X	X	X			X	X	X	X							X	
IMIDs	Thalidomide	X		X		X						X	X		X					X	X	
	Lenalidomide			X	X	X		X		X		X	X	X	X	X				X	X	
	Pomalidomide			X	X	X		X				X	X		X					X		
Chemotherapy	Cyclophosphamide				X	X		X		X			X			X						
	Melphalan				X	X		X					X	X		X						
Corticosteroids	Dexamethasone		X	X						X			X				X		X		X	X
	Prednisone		X	X						X			X				X		X		X	X
DACis	Panobinostat				X	X	X	X			X	X		X								
	Vorinostat				X			X				X	X	X								
mAbs	Elotuzumab							X			X	X	X	X			X	X				
	Daratumumab				X				X									X				

NK natural killer, *PN* peripheral neuropathy, *VTE* venous thromboembolism

Colson K. Treatment-related symptom management in patients with multiple myeloma: a review. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* May 2015;23(5):1431-1445.

Important Factors When Providing Care: Assessment and Management in MM

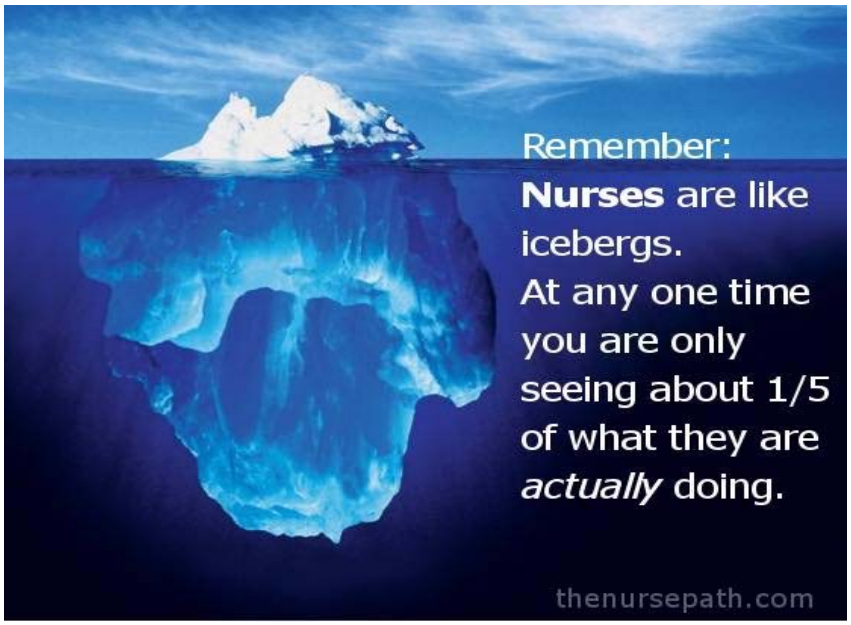
Cardiovascular/VTE	Risk of VTE on IMiDs; Cardiac monitoring (carfilziomib, panobinostat, doxorubicin)	
Bone	Imaging yearly, Do they require bisphosphonates, and for how long? Regular dental exams; Vitamin D, Calcium	
Infectious diseases	Is your patient at high risk for infection? (neutropenia; hypogammaglobulinemia) (myelosuppression from disease/treatment)	– Weekly CBC, differential for 8 weeks with lenalidomide, pomalidomide – HSV prophylaxis with bortezomib, carfilzomib – IV Ig for recurrent infections (a result of hypogammaglobulinemia)
GI	Antiemetic prior to treatment , antidiarrheal agent, laxatives	Assess for diarrhea (bortezomib, lenalidomide), constipation (thalidomide, doxorubicin)
Neurologic	Review increased risk of PN with bortezomib and thalidomide	Prompt intervention can prevent irreversible PN symptoms
Renal	Avoid renal toxic agents, 24-hour urine albumin (bisphosphonates), dose reduction (lenalidomide, melphalan, opioids, acyclovir)	
Disease Monitoring	SPEP, UPEP, 24-hour urine, sFLC monthly	
Health Maintenance	Cancer and cardiovascular surveillance	
Survivorship	Financial, psychosocial issues (years life lost, retirement); Adherence to appts, drugs	

VTE = venous thromboembolism; IMiDs = immunomodulatory drugs; MM = multiple myeloma; CBC = complete blood count; HSV = herpes simplex virus; IV = intravenous; Ig = immunoglobulins; GI = gastrointestinal; PN = peripheral neuropathy; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis; sFLC = serum free light chain.
Kyle et al, 2007; NCCN, 2015; Smith et al, 2008: Faiman et al, 2011; Miceli et al, 2011; Kurtin, 2013.

Conclusion

- Explosion of new therapies to treat MM
- Nurses are positioned to educate patients, identify and intervene side effects
- Knowledge of the drugs and class effects allow for better education, surveillance and continued therapy
- Research is desperately needed to inform sequencing of agents

Questions



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