



*Accredited Educational Activities for  
Advanced Practitioners in Oncology*

# **Collaborative Practice in the Management of Patients With Cancer**

## **Adjunctive and Supportive Care in Multiple Myeloma**

# Program Chair

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# 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

# ADJUNCTIVE AND SUPPORTIVE CARE IN MM

# NCCN Recommendations for Adjunctive Treatment

- **Infection**
  - IVIG for recurrent infections
  - Pneumovax and influenza vaccine
  - PCP, herpes and antifungal prophylaxis for high-dose or long-term steroids
  - Herpes zoster prophylaxis with bortezomib
- **Bone disease**
  - Bisphosphonates
  - Radiation therapy
  - Orthopedic consultation
  - Vertebroplasty or kyphoplasty
- **Renal dysfunction**
  - Avoid aggravating factors: contrast, NSAIDs, dehydration
  - Not a contraindication to HCT
  - Monitor bisphosphonates closely
- **Coagulation/thrombosis**
  - Prophylactic anticoagulation with IMiDs
- **Hypercalcemia**
  - Hydration, steroids, furosemide
  - Zoledronic acid preferred
- **Hyperviscosity**
  - Plasmapheresis
- **Anemia**
  - Consider erythropoietin
  - Transfusion
  - Type and screen patients prior to daratumumab administration

# Prevention and Treatment of Neutropenia and Infections

- Establish a plan for close monitoring of blood counts in initial phase of treatment where risk is greatest
- Review reportable signs and symptoms with patient and caregivers, including who to contact and how
- IVIG for serum IgG < 500
- Immunizations:
  - Poor response to pneumococcal and influenza vaccines (STILL GIVE)
  - **DO NOT GIVE** herpes zoster vaccine
- Shingles prophylaxis:
  - Acyclovir is recommend for all proteasome inhibitor therapy
- Prompt identification of symptoms and institution of treatment
- Subsequent treatment may require dose modification, dose delay, or administration of G-CSF agents as secondary prophylaxis
- Treatment for fungal infections using azoles based on response and tolerance

# Bone Disease

- Malignant plasma cells produce cytokines
- Increase osteoclast differentiation
- Suppress osteoblast maturation
- Inhibit new bone
- Results
  - Infiltrate and destroy bone
  - Secondary effects

## Common presenting symptoms

- Bone pain
- Pathological fractures
- Hypercalcemia



Images courtesy of Sandra Kurtin, RN, MS, AOCN®, ANP-C.



NCCN v3, 2016; Anderson et al., *J Natl Compr Canc Netw* 2015;13:1398–1435; Colson, 2015; *Support Care Cancer* 23(5):1431-1445; Zangari, M. et al (2016). The effects of proteasome inhibitors on bone remodeling in multiple myeloma. *Bone*.

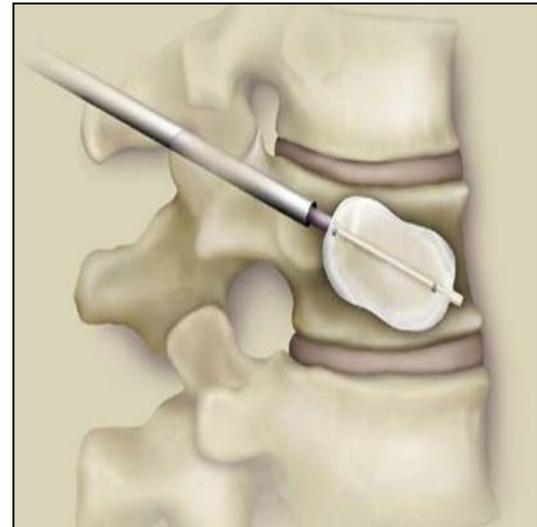
# Management of Bone Disease

- Treat the myeloma
- Novel therapies have benefit:
  - Direct effect on inflammatory cytokines
  - Inhibition of bone resorption
  - Osteoblast stimulation
- Radiotherapy (low dose)
  - Impending fracture
  - Cord compression
  - Plasmacytomas
- Orthopedic consultation
  - Impending or actual long-bone fractures
  - Bony compression of spinal cord
  - Vertebral column instability

Treating the underlying disease and managing any symptoms of clinical findings that require immediate intervention are the goals for managing MM bone disease

# Management of Bone Disease: Supportive Care

- Bisphosphonates (category 1)
  - Pamidronate
  - Zoledronic acid
  - Both require monitoring
    - Renal function
    - Osteonecrosis of jaw
- Kyphoplasty/vertebroplasty
- Home safety evaluation
- Pain management
- Use of spinal support (braces) may be indicated
- Ongoing evaluation of bone health



Kyphoplasty uses a “balloon” to create a cavity for bone cement to reduce vertebral fracture and pain

# IMWG Recommendations for Use of Bisphosphonates in MM

Factor	2013 Recommendation
Patient population	Newly diagnosed patients with MM who require antimyeloma treatment (regardless of bone status)
Administration	IV
Duration/frequency	Monthly during initial therapy and ongoing in patients who are not in remission  After 2 years, discontinue if CR/VGPR; continue if $\leq$ PR
Monitoring	Monthly creatinine clearance
Choice	Zoledronic acid (first option) Pamidronate (second option)

CR = complete response; IV = intravenous; MM = multiple myeloma; PR = partial response; VGPR = very good partial response.

# Bisphosphonate Use in MM: Adverse Events

- Flu-like symptoms
- Fever, myalgias, arthralgias
- Occurs usually 12-48 hours following infusion; lasts 6-24 hours
- Occurs in minority of patients (10%-20%)
- Generally reduced with continued dosing
- Slow rate of infusion and use of steroids and antihistamines may help reduce intensity

Pamidronate: Use in Renal Patients	
Creatinine clearance (mL/min)	Dosing (mg) 90 mg/500 mL NS IV
>30	2-4 hours
<30	Not recommended

Zoledronic Acid: Use in Renal Patients	
Creatinine clearance (mL/min)	Dosing (mg)
>60	4.0
50-60	3.5
40-49	3.3
30-39	3.0
<30	Not recommended

NS = normal saline; IV = intravenous.

NCCN, 2016 v3 ; Terpos et al, 2013, *Blood* **121**(17): 3325-3328; Aredia prescribing information, 2012; Zometa prescribing information, 2014.

# Osteonecrosis of the Jaw (ONJ)

- Baseline dental exam prior to starting bisphosphonate treatment
  - Dental procedures (below the gum line/extensive) should be done prior to starting IV BPs if possible
  - If below the gum line procedures are necessary – hold bisphosphonates 2 months prior to and after procedures
- Avoid unnecessary dental procedures once IV BPs start
- There is no standard treatment: prevention is key
  - Excellent oral hygiene is best prophylaxis
  - Limit alcohol and tobacco use
  - Consider supplementation with calcium 1,000 mg/day and vitamin D 400 IU/day

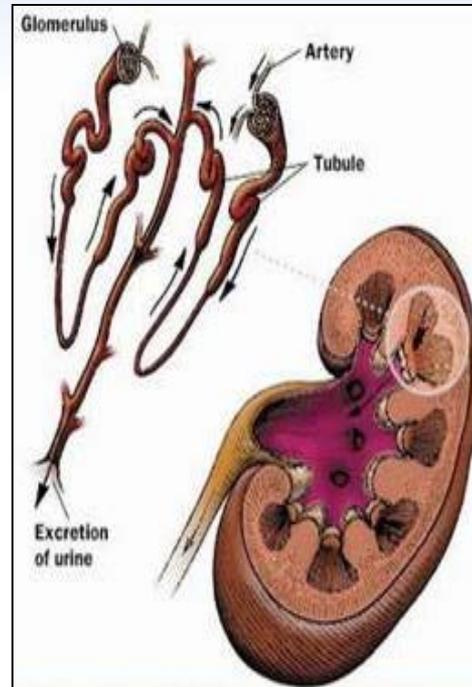


Long-term use of bisphosphonates (> 2.5 years) increases the risk for development of ONJ

# Renal Disease in Multiple Myeloma

## MM Factors

- 2%-40% of patients
- Cast nephropathy
- Hypercalcemia
- Hyperviscosity
- Light chain deposition
- Amyloidosis



## Contributing Factors

- Dehydration
- Hyperuricemia
- Medications
  - Loop diuretics
  - NSAIDs
  - Contrast media
  - Active therapies for MM
  - Bisphosphonates

## Measure of Renal Disease in MM

- Serum creatinine > 2 mg/dL
- Calcium levels > 12 mg/dL
- Elevated free light chains
- Uric acid

**Treatment of the multiple myeloma is often the best strategy to improve renal function**

# Renal Considerations in MM

- Treatment of hypercalcemia
  - Hydration
  - Dexamethasone
  - Diuretics
  - Bisphosphonates
- Treatment of hyperviscosity
  - MM therapy
  - Plasmapheresis
- Coordination with dialysis schedule
  - All agents are administered after dialysis with the exception of ixazomib, which is not dialyzable
- Avoidance of aggravating factors
  - Dehydration
  - Diabetes
  - Hypertension
  - Medications (NSAIDs, loop diuretics)
  - IV contrast

# Renal Considerations in MM: Novel Therapies

## Thalidomide

- No dose adjustment required
- May be associated with hyperkalemia
- Administer after dialysis

## Lenalidomide

- Excreted substantially by the kidney
- Dose adjustments required
- Adverse events may be increased with renal impairment
- Administer after dialysis

## Pomalidomide

- Dose adjustment required in severe renal impairment
- Administer after dialysis

## Bortezomib

- No dose adjustment required
- Dialysis may reduce concentrations, administer after dialysis

## Carfilzomib

- No dose adjustment required
- Dialyzability unknown, administer after dialysis

## Ixazomib

- No dose adjustment required
- *Not dialyzable*

## Panobinostat

- No dose adjustments required
- Dialyzability unknown, administer after dialysis

# Risk Factors for Thromboembolism

## Individual Factors

- General
  - Age
  - Obesity or diabetes
  - Cardiovascular or renal disease
  - Acute infection
- Inherited thrombophilic abnormalities
  - Protein C deficiency, protein S deficiency, factor V Leiden mutation
  - Elevated homocysteine levels
- Central venous catheter use
- Prior DVT, PE, or superficial vein thrombosis

## Disease-Related Factors

- Diagnosis of MM
- Anesthesia, surgery, trauma, or hospitalization
- Immobilization, sedentary lifestyle, extremity paresis
- Other malignant neoplasm
- Hyperviscosity

## Treatment-Related Factors

- High-dose dexamethasone
- Thalidomide, lenalidomide, pomalidomide
- Adjuvant doxorubicin for other cancer
- Multiagent chemotherapy
- ESA use

# Prevention of Thrombosis

- Low risk
  - 0 or 1 risk factor
  - Thromboprophylaxis
    - Low-dose aspirin (81-100 mg/d) is effective if used consistently
- High risk
  - $\geq 2$  risk factors
  - Thromboprophylaxis
    - LMWH or warfarin with therapeutic dosing (INR 2-3)

***Evaluating VTE risk and implementing risk-adapted VTE prophylaxis is a critical prevention strategy in MM***

# Thromboembolic Events: Prophylaxis

- Mechanical
  - Ambulation, exercise is the most effective prophylactic strategy
  - Sequential compression devices
  - Anti-embolism stockings: questionable
- Steroid dose reduction
  - Decreased risk of venous thromboembolism in ECOG trial
  - Dexamethasone reduced dosing 40 mg weekly
    - Deep vein thrombosis: 26% high-dose vs. 12% low-dose ( $P = 0.0003$ )
    - Infection/pneumonia: 16% high-dose vs. 9% low-dose ( $P = 0.04$ )

# Neuropathy

## General Considerations

- Neuropathy may be due to the disease itself due to the overproduction of myeloma proteins
- Patient specific factors may also contribute to neuropathy
- Treatment related neuropathy, most often sensory in nature, is drug specific

## Most Common Symptoms

- Sensory deficits
- Neuropathic pain

## Patient-Related Factors

- Endocrine disorders
  - Hypothyroidism
  - Diabetes
- Nutritional disease
- Connective tissue disease
- Vascular disease
- Medications
- Herpes zoster

## Disease- and Treatment-Related Factors

- Hyperviscosity syndrome
- Hypergammaglobulinemia
- Incidence of peripheral neuropathy in untreated patients: 39%

# Neuropathy

Incidence of grade 3/4 CIPN with novel agents:

## Bortezomib

- Untreated MM: grade 3 = 12%; grade 4 = 1%
- Relapsed/refractory MM: grade 3 = 7%; grade 4 = <1%
- Relapsed/refractory MM (SC vs. IV): grade 3 = 5% SC, 14% IV; grade 4 = 1% SC, 1% IV
- **↓ with weekly vs. twice weekly dosing**
- **↓ with SC administration**

## Thalidomide

- Study 1: neuropathy-sensory grade 3/4 = 4%; neuropathy-motor grade 3/4 = 8%
- Study 2: peripheral neuropathy NOS grade 3/4 = 3%
- ↑ with higher doses and prolonged therapy

## Carfilzomib

- All events of peripheral sensory neuropathy and peripheral motor neuropathy = 14%; grade 3 = 1%

## Ixazomib

- All events of peripheral neuropathy = 18%; grade 3 = 2%

CIPN = chemotherapy-induced peripheral neuropathy; SC = subcutaneous; IV = intravenous; NOS = not otherwise specified.

Kurtin & Billotti, 2013; Colson, 2015; Gleason et al, 2010; Velcade prescribing information, 2012; Thalomid prescribing information, 2013; Kyprolis prescribing information, 2012.

# Management of Neurotoxicity Symptoms

- Baseline and ongoing evaluation
  - Include high-risk comorbidities
- Dose reduction, delay, or omission of drug
  - Agent-specific guidelines
  - Administer bortezomib SC
- Use of various supplements
  - Avoid green tea or vitamin C with bortezomib administration
  - Daily doses of B<sub>6</sub> should not exceed 100 mg
- Emollient creams (e.g., cocoa butter, menthol, and eucalyptus-based)
- Physical therapy
- Stress reduction
- Cognitive behavioral therapy
- Acupuncture
- Pain also may be treated with gabapentin, tricyclic antidepressants, or other agents helpful in relieving neuropathic pain

# Tools for Management of Fatigue

- Individualized assessment
  - Sleep, nutrition, depression, medications, activity, comorbidities
- Individualized interventions
  - Balance between activity and energy conservation
  - Psychosocial interventions
  - Nutrition consultation
  - Sleep evaluation
  - Pharmacologic interventions
    - Psychostimulants, sleep medications

# Strategies for Staying Well

- Eat a balanced diet
- Get daily activity/exercise
- Avoid infection
- Avoid bleeding or clotting
- Continue to enjoy things you love...  
in other words, LIVE
- Get enough rest
- Take advantage of available resources
- Ask for help when needed

# Summary

- Although currently not curable, the median overall survival for multiple myeloma has improved dramatically over the last decade
  - Understanding of the pathobiology of the disease will improve the rationale of supportive care requirements
- Improved long-term survival is the goal
  - Early depth of response → sustained response with an acceptable level of toxicity
- Many new agents are on the way, many will be oral
- Collaborative clinical management together with patient and caregiver empowerment will promote the best outcomes and preserve future treatment options