ADVANCES IN MULTIPLE MYELOMA

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How the Experts Treat Hematologic Malignancies
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Disclosures

• Amrita Krishnan has an affiliation with Celgene Corporation and Janssen Pharmaceuticals (Consultant and Speaker’s Bureau) She is also serves on the Speaker’s Bureau for Millennium Pharmaceuticals and Onyx Pharmaceuticals, Inc.

• Christina Pierce serves on the Speaker’s Bureau for Celgene Corporation and Onyx Pharmaceuticals, Inc.
Objectives

- Epidemiology of Multiple Myeloma
- Clinical presentation and diagnostic testing for newly diagnosed MM
- Staging of MM
- Management strategies of MM
- Review each class of medications for the treatment of MM including assessment and management of adverse reactions
- Review advances in novel therapies for MM including monoclonal antibodies
What is Multiple Myeloma?

- A proliferation of plasma cells that through a complex series of genetic changes, mutations and alterations within the bone marrow microenvironment, they become malignant and produce monoclonal proteins.
- The overproduction of proteins produced by the malignant plasma cells result in depression of the normal functioning immune cells and crowd out the marrow space.
- This process can also result in osteolytic lesions, extensive bony destruction, pathologic fractures and bone marrow failure.
Epidemiology

- New cases in the US in 2015 - 26,850
- Estimated annual deaths - 11,240
- In 2012 there were approximately 89,658 people living with MM
- MM accounts for about 1% of all malignancies
- MM is the 2nd most common hematologic malignancy
- Despite the many advances in the treatment of MM, it remains an incurable disease
Risk Factors

- Race
  - African American 2-3x more prevalent than in Caucasians
  - Lowest risk in Asians, American Indian, Hispanic
- Gender
  - Men > Women
- Age
  - Mean age 62 for Men - 75% >70 years of age
  - Mean age 61 for Women - 79% >70 years of age
- Family
  - Rare cases of familial association in first degree relatives
- Obesity
- Chemical/Radiation exposure

Clinical Presentation

Most common signs and symptoms at presentation:

• Anemia 73% - Hgb<12 related to bone marrow infiltration or renal disease
• Bone Pain 58% - Mostly occurs in back and chest/ribs
• Renal insufficiency 48% - light chain nephropathy and hypercalcemia
• Fatigue/Generalized weakness 32% - related to anemia
• Hypercalcemia 28% Serum CA>11
• Unexplained weight loss 24%

Diagnostic Testing- Laboratory Tests

• CBC with differential
• CMP-Creatinine, calcium, albumin
• LDH- lactate dehydrogenase
• Quantitative Immunoglobulins- IgG, IgA, IgM, IgD
• Free Light Chains
• Serum Protein Electrophoresis (SPEP)/M protein with immunofixation
• Beta-2 Microglobulin
• 24 hour urine- Total protein, UPEP with immunofixation, Light chains
• Serum viscosity- if M protein is high

NCCN guidelines 2016
Diagnostic Testing - Bone Marrow Biopsy

- Morphology
- Immunophenotyping
- Flow Cytometry
- Cytogenetics
- FISH- Fluorescent in Situ Hybridization
- Minimal Residual Disease
  - Post therapy
Diagnostic Testing - Radiographic Studies

- **Skeletal Survey** - Reveal punched out lytic lesions or pathologic fractures
- **CT Scan** - detect lytic lesions, evaluate soft tissue masses
- **MRI** - shows degree of bone destruction, evaluate for cord compression
- **PET/CT** - localize extramedullary disease in non secretory disease
Skeletal Survey Findings

Multiple lytic lesions of the skull

Pathological fracture of R. Humerus
<table>
<thead>
<tr>
<th>MGUS</th>
<th>Smoldering</th>
<th>Active MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum monoclonal protein &lt;3g/dl</td>
<td>M-Protein &gt; 3 g/dl and/or M-protein present in serum or urine</td>
<td></td>
</tr>
<tr>
<td>Clonal BM plasma cells &lt;10%</td>
<td>10-60% plasma cells in the bone marrow plus</td>
<td>&gt; 10% clonal plasma cells in the BM</td>
</tr>
<tr>
<td>Absence of CRAB criteria/ End organ damage</td>
<td>Absence of CRAB/ End organ damage</td>
<td>Myeloma related organ damage (CRAB)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C-Calcium elevation (Ca&gt;10.5 mg/l)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R-Renal Insufficiency (Cr &gt;2 mg/dl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A-Anemia (Hbg &lt;10g/dl)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B-Bony Lytic lesions</td>
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</tbody>
</table>

Myeloma Defining Event - 1 or more of the following  
> 60% clonal plasma cells in BM  
FLC ratio >/= 100mg/L  
MRI with more than 1 focal lesion involving the bone or bone marrow

Risk of progression to MM 1% per year  
Risk of progression to MM 10% per year
Pathogenesis

# Risk Stratification

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH Del 17p t(14;16) or t(14;20)</td>
<td>FISH t(4;14) Cytogenetic del 13</td>
<td>FISH t(11;14) FISH t(6;14) All others</td>
</tr>
<tr>
<td>Median OS 3 years</td>
<td>Median OS 4-5 years</td>
<td>Median OS 8-10 years</td>
</tr>
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### Revised International Staging System for Multiple Myeloma

<table>
<thead>
<tr>
<th>ISS Stage 1</th>
<th>ISS stage II</th>
<th>ISS stage III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum B2-microglobulin &lt;3.5</td>
<td>Serum B2-microglobulin level &gt;5.5</td>
<td></td>
</tr>
<tr>
<td>Albumin &gt; 3.5</td>
<td>Not ISS stage I or III</td>
<td></td>
</tr>
<tr>
<td>Standard risk CA by FISH</td>
<td>High risk CA by FISH or</td>
<td></td>
</tr>
<tr>
<td>Normal LDH</td>
<td>High LDH</td>
<td></td>
</tr>
<tr>
<td>5yr OS rate 82%</td>
<td>5yr OS rate 62%</td>
<td>5yr OS 40%</td>
</tr>
<tr>
<td>5yr PFS rate 55%</td>
<td>5yr PFS rate 36%</td>
<td>5yr PFS rate 24%</td>
</tr>
</tbody>
</table>

Overall Survival by Date of Diagnosis

Patients ≤ 65 years at Diagnosis*

 Patients > 65 years at Diagnosis*

*Swedish Registry data.

Initial Treatment

• Goals of therapy
  – Rapid control of disease
  – Treat and reverse complications of disease
  – Minimal and manageable toxicity from treatment

• Factors to consider with treatment choice
  – Transplant or non transplant candidate
  – High risk disease features
  – Age- fitness/frailty
  – Comorbid conditions- diabetes, heart disease, renal disease
  – Social/financial situation

Treatment Modalities

- Approved MM drug therapies
- High Dose Chemotherapy with Stem Cell Transplant
  - Autologous, Tandem, or Allogeneic
- Surgery
- Radiation
- Supportive care
- Bisphosphonates
- Clinical trials – New and emerging treatments
Diagnosis
- Survival: 3–5 yrs.
- Survival: <6 mos. without Rx
- >11,000 deaths/year

Relapsed disease
- Transient response
- Survival: 1–3 yrs.

Relapsed/refractory disease
- Shorter TTP
- Survival: 6–9 mos.

Salvage therapy
- Repeat primary therapy (if TTR >6 mos.)
- Cyclophosphamide VAD
- Etoposide, dex, cytarabine, cisplatin
- Thalidomide ± dex
- Lenalidomide ± dex
- Bortezomib ± dex; bendamustine
- Bortezomib combinations (eg, liposomal doxorubicin)
- Other novel therapies (clinical trials)

Stem cell harvest, subsequent ASCT (single vs. double) ± maintenance therapy (thalidomide, bortezomib, lenalidomide)
Investigational therapy (allo-SCT)

Initial therapy
- Cyclophosphamide
- Melphalan, prednisone + thalidomide
- + bortezomib
- + lenalidomide
- Thalidomide + dex
- Bortezomib + dex
- Bortezomib combinations
- Bortezomib + liposomal doxorubicin
- Bortezomib + lenalidomide + dex
- Lenalidomide + dex

Rx = prescription; TTP = time to progression; dex = dexamethasone; TTR = time to relapse; VAD = vincristine, doxorubicin, dexamethasone; allo = allogeneic; ASCT = autologous stem cell transplant.

Phases of Multiple Myeloma

IMiDS- Immunomodulatory Agents

Thalidomide (Thalamid)
Lenalidomide (Revlimid)
Pomalidomide (Pomalyst)
Molecular Structure of IMiDs

Thalidomide
100-200 mg/d
Neuropathy
Constipation
Sedation
DVT

Lenalidomide
15-25 mg/d
Myelosuppression
Skin rash
DVT

Pomalidomide
1-4 mg/d

They are structurally similar but functionally different, both qualitatively and quantitatively.

DVT = deep vein thrombosis.
Thalidomide

- 1st IMiD approved in 2006 for first line treatment of MM
- Indicated in combination with dexamethasone for treatment of MM
- Dose: 200mg PO daily with dexamethasone on Day 1-4, 9-12 and 17-20
- Most common AR: Fatigue, hypocalcemia, edema, constipation, neuropathy, dyspnea, muscle weakness, rash/desquamation, confusion, anorexia, nausea, anxiety/agitation, tremor, fever, wt loss, thrombosis/embolism, wt gain, dizziness, dry skin
- Warnings:
  - REMS: Embryo-fetal toxicity
  - Muscle weakness, cytopenias, rash, neuropathy, somnolence, thromboembolism (deep vein thrombosis or pulmonary embolus)
- Nursing considerations: discuss common side effects, assure that pts are taking VTE prophylaxis, assess for neuropathy
Lenalidomide

- Thalidomide analogue, approved in 2006 as 2nd line
- Used in combination with dexamethasone for treatment of MM, in patients who have received at least 1 prior treatment
- Dose: 25mg PO daily days 1-21 in a 28 day cycle
- Most Common AR: URI, dyspnea, nausea, constipation, diarrhea, fatigue, cytopenias, rash, dizziness, muscle cramp, tremor, peripheral edema, and pyrexia,
- Warnings:
  - REMS- Embryo - fetal toxicity
  - Hematologic toxicity - neutropenia and thrombocytopenia
  - Venous thromboembolism - DVT or PE
  - Can impair Stem Cell mobilization
  - Secondary Malignancies
- Nursing Considerations: VTE prophylaxis, REMS, assess/manage AR
Venous Thromboembolus with use of IMiDs

- Reported DVT or PE in 11.6%-21.5% without prophylaxis
- Asa 81mg or 325mg
- Warfarin (INR 2-3)
- Enoxaparin 40mg SQ daily
- Evaluate risk factors: age, obesity, prior history of DVT or PE, immobilization or hyper viscosity
- Nursing Consideration: Assess for swelling and/or breathing difficulties, educate patients and report findings
Pomalidomide

- Newest Thalidomide analogue
- Approved in 2013 for MM in combination with dexamethasone. Patients should have received 2 lines of therapy including lenalidamide and bortezomib and have disease progression on or within 60 days of completion of last therapy
- Dose: 4mg PO daily days 1-21 on a 28 day cycle
- Common AR: cytopenias, pneumonia, fatigue, back pain, constipation, diarrhea, dyspnea, URI, pyrexia.
- Warnings: REMS and VTE risk
- ORR in dual-refractory MM was 30%, median PFS 4 months
- Ongoing clinical trials using it in various combinations with other novel agents with promising results
- Nursing Considerations: DVT prophylaxis, monitor/manage AR, REMS program
Proteasome Inhibitors

Bortezomib (Velcade)
Carfilzomib (Kyprolis)
Ixazomib (Ninlaro)
Proteasome Inhibition

Proteasome inhibitors block the proteasome, producing conflicting regulatory signals and interfering with critical cellular functions.

Cancer Cells can't process overload of conflicting cellular regulatory signals. Cancer Cells undergo apoptosis.

Normal Cells are less sensitive than cancer cells to proapoptotic effects. Normal Cells can recover.

Adapted from Dalton, WS. Medscape. The Proteosome.
Bortezomib

- Approved in 2008 for first line treatment of MM and 2014 for retreatment of Relapsed MM
- Effective in patients with t(4;14)
- Dose: 1.5mg/m2 weekly or 1.3 mg/m2 biweekly
- Route: IV or Subcutaneous
- Common AR: peripheral neuropathy, N/V, diarrhea, cytopenias, fatigue, neuralgia, rash, pyrexia, anorexia, constipation
- Warnings: Peripheral Neuropathy and Hypotension
- Nursing Considerations: Risk for VZV, Viral prophylaxis indicated, Assess PN and other AR, monitor blood counts.

Velcade PI, 2014.
Peripheral Neuropathy- SC vs. IV

- Bortezomib 26%-44%
- Decreased incidence of PN with weekly dosing
- SQ administration approved in 2012
  - Reduced neuropathy with SC administration 6% vs. 15%
  - Reduced GI toxicity
- Skin reactions 6% of patients with erythema, resolved in about 6 days
  - Injection technique - “Air Sandwich”
  - Education - Apply hydrocortisone 1% cream to affected area for erythema/pruritus
- 67.8% patients prefer this route
  - 54 less min of “chair time” and 46 min less clinic time

Managing Peripheral Neuropathy

• Nursing considerations
  – Monitoring for PN
  – Patient Education
• Dose reduction, discontinuation, route of administration
• Interventions- No controlled studies specific to MM
  – Gabapentin, pregabalin
  – Duloxetine
  – Vitamins
    • Alpha Lipoic acid, Vitamin B Complex
  – Opioids
  – Topical Therapy-
    • Combination of baclofen, amitriptyline, and ketamine
    • Menthol cream or cocoa butter
  – Physical Therapy/Occupational Therapy
Carfilzomib

• Second generation proteasome inhibitor
• Approved in 2012 for the indication of Relapsed Refractory MM as a single agent who have received prior therapy with a PI and IMiD and progressed in last 60 days
• Recently approved for use in combination with lenalidomide and dex (KRD)
• First cycle 20mg/m2 Day 1,2 followed by 27mg/m2 day 8,9,15,16
• Then 27mg/m2 Day 1,2,8,9,15,16 followed by 12 day rest period
• Cycle 1 hydration and pre-medicate with dexamethasone 4mg IV
• Common AR: cytopenias, fatigue, nausea, dyspnea, pyrexia, diarrhea, muscle spasm, cough, hypokalemia, URI
• Warnings: Cardiac toxicity, ARF, TLS, Pulmonary hypertension, Dyspnea, VTE, infusion reaction, TTP/HUS, thrombocytopenia, PRES
• Nursing Considerations: VTE prophylaxis, VZV prophylaxis, check blood counts, assess/manage AE
Carfilzomib - Cardiac Toxicity

• Incidence of MI, CHF or other cardiac toxicities occurred in 5% of patients
• Baseline Echocardiogram
• Careful consideration in patients with cardiac comorbidities
• Trial excluded NYHA III or IV CHF, recent MI, uncontrolled arrhythmias
• Hydration pre and post only indicated for first cycle then as needed for subsequent cycles
• Nursing Considerations:
  – Educate patients to report symptoms
  – Monitor for fluid overload
Ixazomib

- 1st oral proteasome inhibitor
- Indicated for treatment of relapsed MM in combination with lenalidomide and dexamethasone
- Dose: 4mg PO on Days 1, 8, and 15 of a 28 day cycle
  - Administer 1 hour before or 2 hours after food
- Lenalidomide is taken on Day 1-21 and dexamethasone on day 1, 8, 15, and 22
- Warnings: Thrombocytopenia, GI toxicity, PN
- Common AR: diarrhea, constipation, thrombocytopenia, PN, nausea, vomiting, edema, back pain
Ixazomib Adverse Events

• Rash
  – Stop lenalidomide first if does not resolve then hold ixazomib. Dose reduction as indicated
  – Topical therapy or antihistamines

• GI toxicity
  – Diarrhea most common
  – N/V and constipation can also occur
  – Implement supportive care
Ixazomib Phase III Toumaline MM1

- IRd vs. Placebo-Rd
- N=700 patients with relapsed/refractory MM
- Overall Response Rate
  - 78% vs.. 72%
  - CR 12% vs. 6.6%
- Median Duration of Response
  - 20.5 mos vs. 15 mos
- Median time to response
  - 1.1 mos vs. 1.9 mos
Pan-deacetylase Inhibitor

Panobinistat (Farydak)
Panobinostat (Farydak)

- Histone deacetylase inhibitor
- Approved for the treatment of Relapsed/refractory MM in combination with bortezomib and dexamethasone
- Dose: 20 mg capsule 3 times per week with bortezomib 1.3mg/m2 2 times per week. 2 weeks on and 1 week off in a 21 day cycle.
- Dex 20 mg 2 times per week with bortezomib and the day after bortezomib
- Warnings: Severe diarrhea, cardiac toxicities including EKG changes and arrhythmias, Hemorrhage (GI and Pulmonary)
- Common AR: diarrhea, fatigue, nausea, peripheral edema, anorexia, pyrexia, nausea, electrolyte abnormalities, cytopenias
- Approved based on results of PFS of 12 months vs. 8.1 months with Vd
- ORR 58.5% vs. 41.4%
- Nursing Considerations: Assess/manage diarrhea with supportive care, check electrolytes, monitor CBC, EKG, assess for sx of infection

Monoclonal Antibodies

Elotuzumab (Empliciti)
Daratumumab (Daralyx)
Elotuzumab

- Monoclonal antibody targeting the signaling lymphocytic activation molecule 7 (SLAMF7)
- Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have relapsed MM after 1 prior line of therapy.
- Warnings: Infusion reactions, Infections, second primary malignancies, interference with assays used to monitor M-protein.
- Common AR: fatigue, diarrhea, pyrexia, constipation, cough, PN, nasopharyngitis, URI, decreased appetite, pneumonia.
• Elo-Rd vs. Rd
• Enrolled 646 patients with Relapsed/Refractory MM
• Overall Response Rate
  – 79% vs. 66%
• Progression Free Survival
  – 19.4 mos vs. 14.9 mos
Elotuzumab Administration

- Cycle 1 & 2 elotuzumab 10 mg/Kg IV weekly D1, 8, 15, and 22
- Cycle 3 until progression elotuzumab 10 mg/Kg IV on D1 and D15
- Lenalidomide 25 mg D1-21
- Dexamethasone 28 mg PO on days of elotuzumab plus 8 mg given IV prior to elotuzumab infusion
- Cycle 3 until progression dexamethasone 40 mg PO on D8 and D22

Elotuzumab- 
Prevention of Infusion Reaction

- Premeds should be given 60-90 minutes before
  - Tylenol 650-1000 mg
  - Benadryl 25-50 mg PO or IV
  - Ranitidine 50 mg IV or 150 mg PO or Pepcid 20 mg PO or IV
- 1st infusion 0.5 ml/min for 30 minutes, increase to 1 ml/min for 30 minutes. Can increase to max rate of 2 ml/min
- 2nd infusion start at 1 ml/min for 30 minutes, then increase to Max of 2 ml/min
- 3rd and 4th start at 2 ml/min, Max of 2 ml/min
- Subsequent start 2 ml/min and titrate up to Max of 5 ml/min
- Monitor frequent VS, assess for infusion reactions

10% of patients had an infusion reaction. 70% of them occurred during the 1st dose.
- Reaction: fever, chills, HTN, hypotension, and bradycardia
- Immediately stop infusion
- Administer ordered medications Benadryl, Tylenol, Demerol prn
- Once symptoms resolve completely then resume at 0.5 ml/min, continue to titrate up to tolerated rate. If reaction recurs then stop for the day
- Monitor VS q30 minutes for 2 hours after the end of the infusion

Daratumumab

- CD38 is highly and ubiquitously expressed on myeloma cells and at low levels on normal lymphoid and myeloid cells, making it a promising therapeutic target in multiple myeloma (MM)\(^1,2\)

- **Daratumumab** (DARA) is a human monoclonal antibody (mAb) that binds to CD38-expressing malignant cells, inducing cell death through multiple pathways including CDC,\(^3\) ADCC,\(^3\) ADCP\(^4\) and apoptosis\(^5\).

**DARA Mechanism of Action\(^2\)**

CDC: complement-dependent cytotoxicity; ADCC, antibody-dependent cell-mediated cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; NK, natural killer cell; NAD, nicotinamide adenine dinucleotide; CADPR, cyclic adenosine diphosphate-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate.

Daratumumab

- Indicated for patients with Relapsed/Refractory MM who have failed 3 prior lines of therapy including a PI and IMiD
- Common AR: Infusion reaction, Fatigue, pyrexia, pneumonia, nausea, back pain, hypertension, cytopenias, herpes zoster reactivation
- Warnings: Infusion reactions, interference with cross-matching and RBC antibody screening
Daratumumab Monotherapy: Phase 1/2 Study

- During ASCO 2014, data from a first-in-human phase 1/2 study was presented that demonstrated single-agent DARA activity in relapsed/refractory MM patients\(^1\)
  - In phase 1 no maximum tolerated dose was reached (up to 24 mg/kg DARA)
  - In phase 2 patients received either 8 mg/kg or 16 mg/kg DARA
  - ORR was 35% in 16 mg/kg DARA group (including 2 CRs, 1 VGPR, and 4 PRs)
  - DARA was well tolerated


ORR, overall response rate; CR, complete response; VGPR, very good partial response; PR, partial response.
Daratumumab Administration

- Week 1-8 16 mg/kg IV weekly
- Week 9-24 16 mg/kg every 2 weeks
- Weeks 25 and beyond: 16 mg/kg every 4 weeks until disease progression
- Infusion rate:
  - 1\textsuperscript{st} dose: (1000 ml volume) Start at 50 ml/hr for 1 hour, increase 50 ml/hour every hour for max of 200 ml/hour
  - 2\textsuperscript{nd} Dose: (500 ml volume) Start at 50 ml/hr for 1\textsuperscript{st} hour. Escalate only if no reaction occurred during the first 3 hours of the 1\textsuperscript{st} infusion. If no reaction then can increase rate by 50 ml/hr up to max of 200 ml/hr
  - Subsequent doses: (500 ml volume) If no reaction on previous infusion after dose increased to >100 ml/hr then can start at 100 ml/hr and increase by 50 ml/hr up to max of 200 ml/hr.
- Infusion time average 7 hours, 4.6 hrs, and 3.4 hours

Daratumumab- Infusion-Related Reactions

- Infusion-related reactions (IRRs) occurred in 43% of patients and were predominantly grade 1 or 2 (grade 3: 5%; no grade 4)
- IRRs typically occurred during the first infusion
- Only 7% of patients had an IRR at >1 infusion
- The most common IRRs included nasal congestion (12%), throat irritation (7%), cough, dyspnea, chills, and vomiting (6% each)
- No patients discontinued treatment due to IRRs
Daratumumab—Prevention/Treatment of Infusion Reaction

- Pre-Medications - Administer 1 hour prior to infusion
  - Methylprednisolone 100 mg with 1st dose then 60 mg for subsequent doses
  - Acetaminophen 650 mg or 1000 mg and IV or PO Diphenhydramine 25-50 mg

- Post infusion - Day 2 and 3: Prednisone 20 mg
  - Pts with hx of COPD consider inhaled corticosteroids and a long-acting bronchodilator post infusion to prevent bronchospasms

- Infusion reactions
  - 46% occurred in first dose, 5% in 2nd infusion and 4% in subsequent doses
  - Can occur up to 48 hours after infusion but most occurred during or within 4 hours from infusion
  - Symptoms: cough, wheezing, larynx and throat tightness, nasal congestion, hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills

- Treatment of Reaction
  - Stop infusion immediately
  - Notify MD/NP/PA
  - Administer hydrocortisone 50-100mg IV
    • Other supportive measures based on sx
  - Resume infusion only when sx resolved

Daratumumab - Effects on Laboratory Testing

- Interference with determination of MM response
  - May be detected on SPEP and may affect determination of disease response/progression in pts with IgG Kappa MM
    - *May have to use other testing to determine response*
    - *Daratumumab interference reflex assay*
  - May persist up to 6 months after last infusion
    - Masks antibody detection to minor antigens

- Interference with serological testing
  - May result in positive indirect Coombs test
    - *May persist up to 6 months after last infusion*
  - Masks antibody detection to minor antigens

- Type and Screen patients prior to therapy initiation
  - Notify blood banks
  - Can use dithiothreitol (DTT) to treat RBC to disrupt daratumumab binding

- If emergency transfusion is required non-cross-matched RBC’s could be given per blood bank policy

Emerging Treatment Options

- SAR650984 - Monoclonal Antibody targeting CD138
- Marizomib - Proteosome inhibitor
- Oprozomib - oral carfilzomib, Proteosome inhibitor
- Filanesib - Kinesin spindle protein inhibitor
- Dinaciclib - Cyclin dependent kinase inhibitor
- Ibrutinib - Tyrosine kinase inhibitor
- Ricolinostat - HDAC inhibitor