BCOP Clinical Sessions
Welcome!

The BCOP Clinical Sessions are part of the professional development program for the recertification of board-certified oncology pharmacists, approved by the Board of Pharmacy Specialties and cosponsored by the American College of Clinical Pharmacy and the American Society of Health-System Pharmacists (ASHP).
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- Participants who pre-paid the post-test fee for the BCOP Clinical Sessions will have access to the posttest immediately following the session at [www.accp.com/myaccount](http://www.accp.com/myaccount).

- Participants who paid the posttest fee in Las Vegas will receive access no later than December 20.
BCOP Clinical Sessions Posttest Cont.

• Reminders:
  – Post-tests must be submitted by March 1, 2017
  – Participants may only submit the posttest one time.
BCOP Clinical Sessions: Multiple Myeloma and Pediatric CINV

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Pediatric Oncology Clinical Pharmacy Specialist
Memorial Sloan Kettering Cancer Center
New York, New York

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Clinical Pharmacist Practitioner, Myeloma and Lymphoma
University of North Carolina Medical Center, Chapel Hill, North Carolina
Disclosures

Jennifer Thackray:

• I will be discussing the off-label (non-FDA approved) use of medication in pediatric patients
Objectives

• Define the phases of chemotherapy-induced nausea and vomiting (CINV) and recognize the risk factors for CINV in a pediatric patient
• Analyze the safety and efficacy of aprepitant and palonosetron in pediatric patients
• Develop a plan for prevention and treatment of each phase of CINV
• Modify an antiemetic regimen for a pediatric patient with breakthrough CINV
Objectives

• Examine prognostic implications and outline patient-specific treatment for multiple myeloma

• Discuss pertinent literature related to ixazomib, elotuzumab and daratumumab

• Illustrate the current roles in therapy of novel agents to treat multiple myeloma
Management of Pediatric Chemotherapy-Induced Nausea and Vomiting: A Complex Case

Jennifer Thackray, Pharm.D., BCPS, BCPPS
Pediatric Oncology Clinical Pharmacy Specialist
Memorial Sloan Kettering Cancer Center
New York, New York
Time for a Poll

How to vote via the web or text messaging

From any browser

From a text message
How to vote via text message

How's my presentation so far?

- Respond at PollEv.com/ashp
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<table>
<thead>
<tr>
<th>Comment</th>
<th>Votes</th>
</tr>
</thead>
<tbody>
<tr>
<td>It's amazing</td>
<td>152964</td>
</tr>
<tr>
<td>It's incredibly amazing!</td>
<td>152965</td>
</tr>
<tr>
<td>It's aw-right</td>
<td>152968</td>
</tr>
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- It's amazing. 152964
- It's incredibly amazing! 152965
- It's aw-right. 152968
Question 1

What percentage of your pediatric patients experience breakthrough CINV that necessitates a change in therapy (PRN to scheduled, antiemetic switch, addition or escalation)?

- A  > 80%
- B  50 – 79%
- C  20 – 49%
- D  < 20%
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Question 1

What percentage of your pediatric patients experience breakthrough CINV that necessitates a change in therapy (PRN to scheduled, antiemetic switch, addition or escalation)?

A > 80%
B 50 – 79%
C 20 – 49%
D < 20%
Introduction

- Highly emetogenic chemotherapy (HEC) is still associated with ~40% breakthrough CINV
- Higher rate in pediatrics than adults
  - Pathogenesis of CINV
  - Higher emetogenicity of chemotherapy regimens
  - Variability of PK parameters and metabolic profiles

Risk Factors

**Chemo-related factors**
Emetogenicity of regimen
Method of administration

**Radiation-related factors**
Dose and type regimen
Administration schedule
Fractionated or not
Body location
Area of radiation field

**Surgery-related factors**
Type and length of surgery
Anesthetic regimen
Premedication
Gastric distention
Movement post-surgery
Post-op pain and analgesics
Oral intake

Complications

• Physiologic
  – Malnutrition
  – Weight loss
  – Esophageal tears
  – Dehydration
  – Fatigue

• Metabolic
  – Electrolyte imbalances

• Psychological
  – Anxiety
  – Non-adherence
  – Reduced future chemotherapy doses
  – Decreased quality of life

Neurotransmitters

- **Cerebral Cortex**
- **Chemoreceptor Trigger Zone (CTZ)**
  - D₂, 5-HT₃, NK₁, M
- **Vomiting Center (VC)**
  - 5-HT₃, NK₁, D₂
- **Salivation center, abdominal muscles, respiratory center and cranial nerves**
- **Nucleus Tractus Solitarius (NTS)**
  - D₂, H₁, 5-HT₃, NK₁, M
- **GI Tract**
  - 5-HT₃, NK₁

**Receptors:**
- D₂: Dopamine 2 receptor
- 5-HT₃: Serotonin type 3 receptor
- NK₁: Neurokinin 1 receptor (Substance P)
- H₁: Histamine 1 receptor
- M: Muscarinic cholinergic receptor (Acetylcholine)

Current Standard of Care for Prevention of Pediatric CINV
Phases of CINV

**Acute**
- < 24 hours after chemotherapy
- Correlates with administration of chemotherapy

**Delayed**
- > 24 hours following completion of chemotherapy
- Mechanism not fully understood
  - Substance P/NK1 receptors

**Anticipatory**
- Learned reaction
- Cerebral cortex
- Many triggers (smell, sight, touch)

**Breakthrough**
- CINV during the acute or delayed phase despite antiemetic prophylaxis

5-HT₃ RA, Serotonin receptor antagonist; DEXA, dexamethasone; D₂ RA, Dopamine 2 receptor antagonist; OLZ, olanzapine; BZD, benzodiazepine; NK₁ RA, Neurokinin 1 receptor antagonist; PALO, palonosetron; H₁ RA, Histamine 1 receptor antagonist

Refractory CINV

• Not well defined

• N/V during subsequent chemotherapy cycles when antiemetic prophylaxis has not been successful in previous cycles

• If multiple rescues or switches were made, consider upgrading CINV prophylaxis for next cycle

### Standard of Care

#### High Risk (> 90%)
- Carboplatin / Cisplatin
- Cyclophosphamide ≥ 1 g/m²
- Cytarabine (Ara-C) 3 g/m²
- Methotrexate (MTX) ≥ 12 g/m²
- Thiotepa ≥ 300 mg/m²

#### Moderate (30-90%)
- Clofarabine
- Ara-C ≤ 200 mg/m²
- Dauno/Doxorubicin
- MTX 0.25-12 g/m²
- Irinotecan

#### Low (10-30%)
- Etoposide
- MTX 51-250 mg/m²
- Topotecan
- Busulfan (PO)

#### Minimal (< 10%)
- Asparaginase
- Mercaptopurine
- Vincristine
- Vinorelbine

### Prophylaxis

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Children &lt; 12 yr</th>
<th>Children &gt; 12 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minimal</td>
<td>Ondansetron or Granisetron</td>
<td>Aprepitant</td>
</tr>
<tr>
<td>Low</td>
<td>Ondansetron or Granisetron</td>
<td>Ondansetron or Granisetron</td>
</tr>
<tr>
<td>Moderate</td>
<td>Ondansetron or Granisetron</td>
<td>Ondansetron or Granisetron</td>
</tr>
<tr>
<td>High Risk</td>
<td>DEXA</td>
<td>DEXA</td>
</tr>
</tbody>
</table>

HEC: highly emetogenic chemotherapy; MEC: moderately emetogenic chemotherapy; LEC: low emetogenic chemotherapy

Serotonin Receptor Antagonists
(5HT₃RAs)
5-HT\textsubscript{3} Receptor Antagonists

- Cornerstone of acute CINV prophylaxis

- Blocks serotonin peripherally (vagal nerve terminals) and centrally (CTZ)

- Threshold effect for response and modest dose-response curve above specific dose

Ondansetron: 1st Generation 5-HT\textsubscript{3}RA

- First in class
- 2012 FDA label change
  - Peak concentration associated with increased risk of Torsades de Pointes
- Pediatrics: 0.15 mg/kg (max 16 mg) IV Q4H x 3 doses
- IVCI = single dose = multiple daily doses

Granisetron: 1st Generation 5-HT₃RA

- **FDA-labeled dosing**
  - 2 – 17 yr: 10 mcg/kg IV
  - Adults: 10 mcg/kg IV; 2 mg PO daily or divided BID

- **Miyajima, et al**
  - Prospective, crossover
  - GRAN vs. conventional antiemetics
  - GRAN 40 mcg/kg IV 30 min prior to HEC
  - Acute CINV CR = 60% (vs. 0%, p<0.001)

- **Komada, et al**
  - Randomized trial (N=49; Mean age 6.3 yr)
  - GRAN 20 vs. GRAN 40 (HEC)
  - Acute CINV CR > 80% in both groups
  - Similar safety profile

- **2013 POGO Consensus Acute CINV**
  - 40 mcg/kg IV (no max) as a single daily dose prior to HEC/MEC
  - 40 mcg/kg PO BID

Palonosetron: 2\textsuperscript{nd} Generation 5-HT\textsubscript{3}RA

- Peripherally and centrally acting
- Longer duration of action and higher affinity
  - Biologic duration of action = 120 hr (adults)
  - Half-life elimination ~20-30 hr (peds); ~40 hr (adults)
  - Onset of action = 2 hr (adults)
- Toxicity
  - Similar rates of constipation and headache in adults
  - Lower risk of QTc prolongation than first generation 5-HT\textsubscript{3}RAs
- Dosing
  - 1 mon to 16 yr: 20 mcg/kg (max 1.5 mg) IV beginning ~30 min prior to chemotherapy
  - ≥ 17 yr: 0.25 mg IV beginning ~30 min prior to chemotherapy

Palonosetron in Pediatrics

• Phase III, randomized, double-blind, double-dummy, non-inferiority trial
  – 1° endpoint: Non-inferiority of PALO vs. OND for acute CINV ($\delta = -15\%$)
  – 2° endpoints: CR in delayed and overall CINV
  – 493 pediatric patients receiving up to 4 MEC/HEC cycles

• Intervention: Day 1 of chemotherapy
  – PALO 10 mcg/kg IV (n = 166)
  – PALO 20 mcg/kg IV (n = 165)
  – OND 0.15 mg/kg IV Q4H x 3 (n = 162)

Palonosetron in Pediatrics

• Patient characteristics (N = 493)
  – Mean age 8 yr (range 2.5 mon – 16.92 yr)
  – 50% male; 85% white
  – 25% leukemia/lymphoma
  – 25% naïve to chemotherapy
  – 33% HEC; 67% MEC
  – 52% Day 1 chemo only
    – 48% multi-day chemo (up to 6 days)
  – 32% received dexamethasone at some point on days 1 – 6
    – 55% received concomitant corticosteroids
  – Allowed prophylactic antiemetics for chemotherapy after day 1 according to standard of practice

Palonosetron Efficacy & Safety

<table>
<thead>
<tr>
<th>First On-Study Cycle</th>
<th>PALO 10 mcg/kg IV (n = 166)</th>
<th>PALO 20 mcg/kg IV (n = 165)</th>
<th>OND 0.15 mg/kg IV Q4H x3 (n = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (Day 1)</td>
<td>54% (−16.4 – 7.6); p = 0.0242</td>
<td>59% (−11.7 – 12.4); p = 0.0022</td>
<td>59%</td>
</tr>
<tr>
<td>CR(_{0-24h}), 97.5% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed (Days 2-5)</td>
<td>29% (−9.4 – 10.3)</td>
<td>39% (−0.1 – 20.4)</td>
<td>28%</td>
</tr>
<tr>
<td>CR(_{25-120h}), 97.5% CI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall (Days 1-5)</td>
<td>23% (−10 – 8.8)</td>
<td>33% (−16.4 – 7.6)</td>
<td>24%</td>
</tr>
<tr>
<td>CR(_{0-120h}), 97.5% CI</td>
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</tbody>
</table>

- Treatment-emergent adverse events were similar in all three groups (4%)
  - Headache (2%), cardiac (< 1%)

Palonosetron 20 mcg/kg (max 1.5 mg) IV 30 minutes prior to HEC or MEC is non-inferior to ondansetron for **acute, delayed and overall** CINV in 1 mon to 17 years

### PALO: What We Know From Adults

#### Highly Emetogenic Chemotherapy (HEC)

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) DEX</td>
<td>PALO = GRAN (~70%)</td>
<td>PALO (57%) &gt; GRAN (45%)</td>
</tr>
<tr>
<td></td>
<td>PALO = OND (~60%)</td>
<td>PALO (41%) &gt; OND (25%)</td>
</tr>
<tr>
<td>(-) DEX</td>
<td>PALO = GRAN (~68%)</td>
<td>PALO = GRAN (68%)</td>
</tr>
</tbody>
</table>

#### Moderately Emetogenic Chemotherapy (MEC)

<table>
<thead>
<tr>
<th></th>
<th>Acute</th>
<th>Delayed</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+) DEX</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>(-) DEX</td>
<td>PALO (81%) &gt; OND (69%)</td>
<td>PALO (74%) &gt; OND (55%)</td>
</tr>
</tbody>
</table>

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Palonosetron: Summary

  - In acute CIV, PALO+DEX is non-inferior to OND+DEX for control of acute, delayed HEC or MEC

- Popovic, et al 2014 (Adults and Pediatrics)
  - In acute CIV, PALO is comparable to other 5HT₃RAs with DEX (OR 1.14; 95% CI 0.88-1.49)
  - For delayed CINV, PALO is superior to other 5HT₃RAs with or without DEX
    - DEX: OR 1.65; 95% CI 1.31-2.08
    - No DEX: OR 1.57; 95% CI 1.18-2.1

RH is a 4 year-old (18 kg, 110 cm, 0.74 m²) female with osteosarcoma here for cycle 4 of cisplatin and doxorubicin. The antiemetics ordered are palonosetron 0.35 mg IV and dexamethasone 6 mg IV to be given 30-60 minutes prior to chemotherapy. Which of the following is true regarding palonosetron dosing?

A. Underdosed
B. Overdosed
C. Correctly dosed
D. Palonosetron is not safe to be used in pediatrics
Question 2

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A. Underdosed
B. Overdosed
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5HT\textsubscript{3}RA of Choice - Pediatrics

**Ondansetron**
- Most experience
- Highest risk of QTc prolongation?
- Multiple dosing formulations
- Multiple dosing schedules

**Granisetron**
- Weak literature to support pediatric dosing
- Similar safety and efficacy to ondansetron

**Palonosetron**
- FDA-approval for 1 month and older
- Delayed CINV benefit?
- Lowest rate of side effects
- IV only
- Re-dosing information lacking

- Comparative efficacy appears to be affected by the presence of dexamethasone
- Higher doses required for efficacy in pediatric patients
- Similar safety profiles to adult patients, despite higher doses

NK₁ Receptor Antagonist
NK₁ Receptor Antagonist

• Blocks substance P from activating the neurokinin-1 (NK₁) receptors in the CNS

• Augments effects of 5HT₃RAs and dexamethasone

• Potentially significant drug-drug interactions
  – CYP3A4 substrate, inhibitor & inducer
  – CYP2C9 inducer

• Aprepitant recently studied in pediatric patients
The Aprepitant Story

- **Mar 2003**: FDA approves Emend® capsules
- **Dec 2003**: Pediatric Rule challenged in court; FDA couldn’t enforce
- **Sep 2004**: Merck submitted proposed pediatric study request (PPSR) for Emend® capsules for > 2 yr
- **Oct 2005**: FDA waived study requirement for 0 – 6 months of age
- **Feb 2009**: Written Request (WR) issued by FDA for a pediatric study
- **Sep 2011**: Phase III, pediatric aprepitant trial published
- **Mar 2015**: PK data reviewed and FDA-label expanded to < 12 yr & ≥ 30 kg
- **Sept 2015**: Aprepitant oral suspension commercially available
- **Dec 2015**: FDA-approved aprepitant oral suspension for > 6 months of age
- **Oct 2016**: Phase III, pediatric aprepitant trial published

- **Aug 2002**: Pediatric Research Equality Act (PREA) passed → Retroactive
Aprepitant in Pediatrics

• Phase 3, multi-center, double-blind, randomized trial
  – 1° endpoint: CR during delayed phase (CR_{25-120h}) after Day 1 chemotherapy

• Intervention
  – APREP (Days 1-3) + OND (mean duration 3 days)
    – 6 mon – 12 yr: 3 mg/kg PO Day 1, 2 mg/kg Day 2, 3 (powder for suspension)
    – 12 – 17 yr: 125 mg PO Day 1, 80 mg Day 2, 3 (capsules)
  – OND alone (mean duration 2.8 days)
    – Dose according to site (mean 0.18 mg/kg)

Aprepitant in Pediatrics

- Patient characteristics (N = 302)
  - Mean age 7 yr (range 0.5 – 17.8 yr)
  - 55% male; 75% white
  - 40% naïve to chemotherapy
  - 66% HEC; 33% MEC
  - 85% received more than 1 day
    - Most patients received chemo for 3 days (range 1 – 7 days)
  - 28% received dexamethasone (0.05 – 0.44 mg/kg)

# Aprepitant in Pediatrics

|                          | APREP/OND + DEX  
|                          | (n = 152) | OND + DEX  
<table>
<thead>
<tr>
<th></th>
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<th>(n = 150)</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td><strong>Delayed (CR\textsubscript{25-120h}) – ALL</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>HEC</td>
<td>51%</td>
<td>26%</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>No HEC</td>
<td>42%</td>
<td>20%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Acute (CR\textsubscript{0-24h}) – ALL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEC</td>
<td>66%</td>
<td>52%</td>
<td>0.0135</td>
</tr>
<tr>
<td>No HEC</td>
<td>65%</td>
<td>51%</td>
<td>--</td>
</tr>
<tr>
<td><strong>Overall (CR\textsubscript{0-120h}) – ALL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEC</td>
<td>40%</td>
<td>20%</td>
<td>0.0002</td>
</tr>
<tr>
<td>No HEC</td>
<td>35%</td>
<td>14%</td>
<td>--</td>
</tr>
</tbody>
</table>

“HEC” is represented in the trial as ‘VHEC’ and is defined as >90% emetogenic potential
“No HEC” is represented in the trial as ‘No VHEC’ and includes MEC and LEC

Question 3

BT is an 8-year-old (30 kg) male with metastatic osteosarcoma receiving his first cycle of chemotherapy with cisplatin and doxorubicin. Which of the following would be the best regimen for prevention of CINV?

A. APREP + OND + DEX
B. APREP + OND
C. OND + DEX
D. OND only
Question 3

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Question 3

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A. APREP + OND + DEX
B. APREP + OND
C. OND + DEX
D. OND only
Aprepitant: Summary

• Kang, et al 2015 (Pediatrics)
  – APREP + OND + DEX is safe and effective for acute and delayed CINV in patients 6 months and older receiving HEC
  – Efficacy in MEC not delineated
  – Role of dexamethasone undefined
• Capsule: 125 mg, 80mg (>12 yr or >30kg)
• Oral solution
  – Commercial formulation (Oct 2016): 25 mg/mL with 72-hr stability
  – Published extemporaneous compound 20 mg/mL with 90-day stability

Future Standard of Care for Prevention of Pediatric CINV
Current Standard of Care

High Risk (> 90%)

- Carboplatin / Cisplatin
- Cyclophosphamide ≥ 1 g/m²
- Cytarabine (Ara-C) 3 g/m²
- Methotrexate (MTX) ≥ 12 g/m²
- Thiotepa ≥ 300 mg/m²

Moderate (30-90%)

- Clofarabine
- Ara-C ≤ 200 mg/m²
- Dauno/Doxorubicin
- MTX 0.25-12 g/m²
- Irinotecan

Low (10-30%)

- Etoposide
- MTX 51-250 mg/m²
- Topotecan
- Busulfan (PO)

Minimal (< 10%)

- Asparaginase
- Mercaptopurine
- Vincristine
- Vinorelbine

HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; LEC, low emetogenic chemotherapy

- HEC > 12 yr: Aprepitant
  - Ondansetron or Granisetron
  - DEXA
- HEC < 12 yr: Ondansetron or Granisetron
  - DEXA
- MEC: Ondansetron or Granisetron
  - DEXA
- LEC: Ondansetron or Granisetron
  - DEXA
- Minimal: No routine prophylaxis

HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; LEC, low emetogenic chemotherapy

New Standard of Care

**High Risk (> 90%)**
- HEC > 6 mon
  - Aprepitant
  - Ondansetron or Granisetron or Palonosetron
  - DEXA

**Moderate (30-90%)**
- MEC
  - Aprepitant?
  - Ondansetron or Granisetron or Palonosetron
  - DEXA

**Low (10-30%)**
- LEC
  - Ondansetron or Granisetron or Palonosetron

**Minimal (< 10%)**
- No routine prophylaxis

HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; LEC, low emetogenic chemotherapy

Treatment of Breakthrough CINV
Breakthrough CINV

1. PRN
   - Choose drug from a different drug class to give as needed
   - May require multiple agents

2. Add
   - Add ‘as needed’ drug to around the clock
   - Choose drug from a different drug class to give around the clock

3. Switch
   - Rotate drugs within same class
   - Rotate schedule of medication
   - Route has not been shown to be superior

Diphenhydramine
Dronabinol
Haloperidol
Hydroxyzine
Lorazepam
Metoclopramide
Olanzapine
Promethazine
Scopolamine patch

Ondansetron IVCI
Granisetron
Palonosetron

Breakthrough CINV

Did the breakthrough medication control the patient’s nausea and vomiting?

**YES**
Continue breakthrough medication scheduled (not PRN)

**NO**
Add (schedule) a drug from a different drug class* and another PRN medication

Note patient-specific changes for next chemotherapy cycle!

*Continued from the previous chemotherapy cycle.

---

Patient Case 1

- AJ is a 4 year-old girl (20 kg) with high-risk neuroblastoma who is post-op day (POD) 5 from primary tumor resection and starting cycle 4 chemotherapy today:
  - Cyclophosphamide 70 mg/kg IVPB over 6 hr x 2 days
  - Doxorubicin 25 mg/m2 IVCI x 72 hr
  - Vincristine 0.022 mg/kg IVCI x 72 hr

- Prophylactic agents
  - Ondansetron IV continuous infusion
  - Dexamethasone IV daily
  - Lorazepam IV Q6H around the clock

- Breakthrough CINV agents
  - Metoclopramide IV Q6H PRN breakthrough nausea
  - Hydroxyzine PO Q6H PRN breakthrough nausea

On Day 3, AJ has vomited 3 times per day and has been persistently nauseated. Per mom, after receiving hydroxyzine the nausea subsides for “a little bit”

EMR documentation:
Metoclopramide IV x 3 per day
Hydroxyzine PO x 3 per day
Question 4

Which of the following changes should be made to control AJ’s CINV?

A. Add PO aprepitant
B. Change PO hydroxyzine from PRN to scheduled
C. Change IV ondansetron to IV granisetron
D. Change IV metoclopramide to PO olanzapine
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Breakthrough CINV

1. PRN
   - Choose drug from a different drug class to give as needed
   - May require multiple agents

2. Add
   - Add ‘as needed’ drug to around the clock
   - Choose drug from a different drug class to give around the clock

3. Switch
   - Rotate drugs within same class
   - Rotate schedule of medication
   - Route has not been shown to be superior

Diphenhydramine
Dronabinol
Haloperidol
Hydroxyzine
Lorazepam
Metoclopramide
Olanzapine
Promethazine
Scopolamine patch

Ondansetron IVCI
Granisetron
Palonosetron

Decisions, Decisions

- Formulation
- Age / Weight limitations
- Adverse effects
- Neurotransmitter
- Antiemetic of choice
- Compelling indication
Patient Case 2

• An 12 year-old female (40 kg) with Ewing sarcoma presents to clinic for cycle 2 chemotherapy
  – Ifosfamide 2800 mg/m² IVPB over 4 hr x 5 days
  – Etoposide 100 mg/m² IVPB over 1 hr x 5 days

• Antiemetic prophylaxis
  – Aprepitant 125 mg PO Day 1, 80 mg PO Day 2, 3
  – Ondansetron IV
  – Dexamethasone IV
  – Hydroxyzine PO PRN – not taking
  – Metoclopramide IV PRN – not taking overnight

• On Day 3, admitted for dehydration and electrolyte imbalances due to CINV
  – Metoclopramide IV Q6H

Additional Options:
- Dronabinol (PO only)
- Diphenhydramine – *anticholinergic*?
- Famotidine – *GERD*?
- Fosaprepitant (duplicate)
- Granisetron (duplicate)
- Haloperidol (adverse effect; EPS)
- Hydroxyzine (PO only)
- Lorazepam – *Anxiety*?
- Olanzapine (PO only)
- Palonosetron (duplicate)
- Prochlorperazine (adverse effect; EPS)
- Promethazine (PO only)
- Scopolamine (age > 13 yr)
Olanzapine (OLZ)

- Multiple-receptor antagonistic activity in CNS
  - $5\text{-HT}_{2A}$, $5\text{-HT}_{2C}$, D$_{1-4}$, H$_1$ and $\alpha_1$-adrenergic

- Compelling indications
  - Mood elevation, insomnia, anxiety, weight gain

- Clinical considerations
  - EPS risk
  - Serotonin syndrome
  - LFT elevation
  - No IV formulation
OLZ: What We Know From Adults

• OLZ vs. METO
  – BT-CINV in HEC despite FOSAPREP + PALO + DEX
    – OLZ 10 mg PO daily or METO 10mg PO TID (x 3 days)
  – CR (no vomiting) in 72 hr period
    – OLZ 70% (39/56) vs. METO 31% (16/52) p<0.01

• OLZ + PALO + DEX vs. APREP + PALO + DEX
  – Acute CR: 80% (97/121) vs. 73% (87/120); p>0.05
  – Delayed CR: 64% (77/121) vs. 61% (73/120); p>0.05

OLZ: What We Know From Adults

- **NK₁RA + 5HT₃RA + DEX + OLZ (n=380)**
  - 18 years and older receiving HEC
  - Acute CR higher in OLZ group
    - 86% (156/182) vs. 65% (117/181); p>0.001
  - Delayed CR higher in OLZ group
    - OLZ: 67% (109/163) vs. 52% (88/168); p>0.007

Olanzapine for CINV (Adults)

  - HEC/MEC Acute and Delayed Prevention option
    - NK₁RA + 5HT₃RA + DEX
    - OLZ 10 mg PO daily + PALO + DEX
  - Breakthrough CINV options
    - Add OLZ 10 mg PO daily (over metoclopramide)
    - Consider changing from NK₁-containing regimens to OLZ-containing regimen, or vice versa

OLZ for CINV (Pediatrics)

• 20 month, multi-center, retrospective review

• N=60; 159 cycles
  ‒ Median age 13.2 yr (3.1 – 17.96 yr)
  ‒ 50% sarcoma; 20% neuroblastoma; 12% CNS tumors; 10% ALL
  ‒ Mean dose 0.1 ± 0.05 mg/kg/day
  ‒ ADR: 7% sedation, 20% increased LFTs
    ‒ ↑dose = ↑sedation (p=0.0001)

• OLZ started on Day 1 (83% HEC; 128 cycles)
  ‒ 65% acute CIV control

# Pros of Breakthrough CINV Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Acid reflux</th>
<th>Anxiety</th>
<th>Appetite</th>
<th>Constipation</th>
<th>Depressed Mood</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Insomnia</th>
<th>Travel Sickness</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Over the counter</td>
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<tr>
<td>Dronabinol</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td>Over the counter</td>
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<tr>
<td>Haloperidol</td>
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<td>Yes</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoclopramide</td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Oral disintegrating tablet</td>
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<tr>
<td>Palonosetron</td>
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<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Long acting</td>
</tr>
<tr>
<td>Promethazine</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopolamine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
<td>Transdermal patch Q72H</td>
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</table>

## Cons of Breakthrough CINV Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Oral</th>
<th>IV</th>
<th>↓ CNS</th>
<th>↓ WBC</th>
<th>Age/Wt limit</th>
<th>QTc prolonging</th>
<th>EPS risk</th>
<th>Paradoxical effect</th>
<th>Anti-cholinergic</th>
<th>Notes</th>
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</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>Yes</td>
<td>No</td>
<td></td>
<td></td>
<td>≥ 12 yr or ≥ 30 kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Insurance coverage; Drug interactions (CYP3A4)</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dronabinol</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>May ↓ seizure threshold; May worsen psych disorders; Contains sesame oil</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>GERD</td>
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<tr>
<td>Haloperidol</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>≥ 3 yr</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
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<td>Hydroxyzine</td>
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<td></td>
<td></td>
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<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Lorazepam</td>
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<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Anxiolytic; Risk of dependence</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>↑ GI motility</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td></td>
<td>Drug interactions (5HT₃); ↑ LFTs</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td>≥ 1 mon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Constipation; Headache</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
<td>≥ 2 yr</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 2 yr respiratory depression (BBW)</td>
</tr>
<tr>
<td>Scopolamine</td>
<td>No</td>
<td>No</td>
<td></td>
<td></td>
<td>≥ 13 yr</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>Patch contains aluminum (MRI)</td>
</tr>
</tbody>
</table>

Breakthrough CINV

1. PRN
   - Choose drug from a different drug class to give as needed
   - May require multiple agents

2. Add
   - Add ‘as needed’ drug to around the clock
   - Choose drug from a different drug class to give around the clock

3. Switch
   - Rotate drugs within same class
   - Rotate schedule of medication
   - Route has not been shown to be superior

Diphenhydramine
Dronabinol
Haloperidol
Hydroxyzine
Lorazepam
Metoclopramide
Olanzapine
Promethazine
Scopolamine patch

Ondansetron IVCI
Granisetron
Palonosetron

Treatment of Breakthrough CINV

• Patient-specific interventions

• Implement changes for next cycle
  – Communication is key

• Better prevention
  – Focused update regarding optimal aprepitant and palonosetron use in pediatrics
  – To be published Fall 2016
Tips for Evaluating CINV Literature

• Emetogenic classification
  – Rate of control
• Moderate 30 – 90%: Broad range!
• Nausea or vomiting or both
• Type of CINV
• Concomitant steroid use
Barriers to Implementation

• Drug
  – Formulations (liquid not available, IV only)
  – Ages studied (restrictions, labeling)
  – Weak dosing recommendations for pediatrics in older medications

• Hospital
  – Formulary restrictions

• Cost
  – Insurance reimbursement
Looking Forward

• How clinically significant are the drug-drug interactions with aprepitant and chemotherapy?
• Is aprepitant effective and/or necessary for patients receiving MEC?
• Is palonosetron superior to for acute and/or delayed CINV in pediatrics?
• How often can palonosetron be re-dosed?
• Is fosaprepitant safe and effective in pediatrics?
Summary

• The high incidence of breakthrough CINV in pediatrics may decrease in the future as more aggressive CINV medications are studied (aprepitant, palonosetron)

• The 5-HT3RAs are the cornerstone to preventing CINV, however the optimal 5-HT3RA for pediatric patients is yet to be determined

• Pharmacists can play a big role in drug therapy management of CINV by recognizing compelling indications, adverse effects of various antiemetics and making interventions or upgrading prophylaxis for the next cycle
Evolving Treatment Strategies for Multiple Myeloma

Jill S. Bates, Pharm.D., M.S., BCOP, CPP
Clinical Pharmacist Practitioner, Myeloma and Lymphoma
University of North Carolina Medical Center, Chapel Hill, NC
Patient Case

KH is a 46 year old female who presented with lower back pain that came on suddenly after lifting furniture. After several weeks of managing pain at home, KH came in for evaluation where a lumbar magnetic resonance image noted diffuse bony metastasis and compression fractures. Biopsy was obtained, labs as follows:

- Mean Corpuscular Volume: 99
- Calcium: 10.5

\[
\begin{array}{c}
5.1 \\
10 \\
31.1 \\
243
\end{array}
\]
Patient case

Expedited workup of KH ensued. The following data was obtained:
Serum protein electrophoresis (SPEP) with immunofixation: monoclonal kappa free light chains (FLC), IgA kappa. Kappa FLC 637.5 mg/dL.
Bone marrow biopsy: hypercellular marrow with 80% involvement by plasma cell neoplasm. Monotypic kappa, CD138+.
FISH: FGFR3 deletion.
Routine cytogenetics: 46, XY.
Beta-2 microglobulin 3.07, albumin 4.5, Lactate dehydrogenase (LDH) 522
Question 5

Which of the following best describes KH’s diagnosis?

A. ISS 1 IgA kappa symptomatic multiple myeloma
B. AL-amyloidosis
C. ISS 2 IgG lambda asymptomatic multiple myeloma
D. plasma cell leukemia

ISS= International Staging System
AL= amyloid light chain
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Multiple Myeloma (MM)

- Estimated new cases of MM in 2016 are 30,330 with 12,650 estimated deaths
- Myeloma carries with it a 6.5% incidence rate (2009-2013), 3.3% mortality rate (2009-2013) and 48.5% survival rate (2006-2012)
- More prevalent in black ethnicity, males, and demonstrates clustering in families
- Median age of onset is 72 years

The Double Hit Hypothesis in MM

Plasmablast/Plasma cell → Plasma cell → Apoptosis normal

HIT #1

Plasmablast/Plasma cell → Plasmablast/Plasma cell no apoptosis

HIT #1

Plasmablast/Plasma cell → Plasmablast/Plasma cell no apoptosis

Plasma cells accumulate
Monoclonal gammopathy of undetermined significance (MGUS)

HIT #2

Plasma cells accumulate (MGUS)

Multiple myeloma

Spectrum of Disease Progression

Normal long-lived plasma cell

Increased DNA-labeling index

MGUS

Germinal center B cell

Smoldering Myeloma

Intramedullary Myeloma

Extramedullary Myeloma

Myeloma

Bone Marrow stromal dependence

Interleukin (IL)-6 dependence

Angiogenesis and bone destruction

## Three Definitions of “Multiple Myeloma”

<table>
<thead>
<tr>
<th>Disease process</th>
<th>Diagnostic criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic multiple myeloma</td>
<td>Monoclonal plasma cells in the bone marrow (≥10%)</td>
</tr>
<tr>
<td></td>
<td>Plasmacytoma</td>
</tr>
<tr>
<td></td>
<td>Presence of monoclonal protein in serum or urine</td>
</tr>
<tr>
<td></td>
<td>Myeloma-related end organ damage (e.g. CRAB)</td>
</tr>
<tr>
<td>Smoldering or indolent myeloma</td>
<td>Monoclonal protein in serum ≥3g/100ml</td>
</tr>
<tr>
<td></td>
<td>Monoclonal plasma cells in bone marrow ≥10% or present in a tissue biopsy</td>
</tr>
<tr>
<td></td>
<td>No evidence of end organ damage related to clonal plasma cells</td>
</tr>
<tr>
<td>MGUS</td>
<td>Serum monoclonal protein &lt;3 g/100ml</td>
</tr>
<tr>
<td></td>
<td>Monoclonal plasma cells in the bone marrow &lt;10%</td>
</tr>
<tr>
<td></td>
<td>No evidence of end organ damage related to clonal plasma cells</td>
</tr>
</tbody>
</table>

Myeloma-related Organ or Tissue Impairment

- Hyperviscosity
- Infection
- Spinal cord compression
- hyperCalcemia
  - Renal dysfunction
  - Anemia
  - Bone lesions

## Laboratory Evaluation

<table>
<thead>
<tr>
<th>Test</th>
<th>Type of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electrophoresis</td>
<td>Method of separating proteins based on their physical properties. Can be used to identify a band of restricted mobility or M-spike.</td>
</tr>
<tr>
<td>Quantitative immunoglobulins</td>
<td>Measures the quantity of different immunoglobulins using either nephelometry or tubidimetry.</td>
</tr>
<tr>
<td>Immunofixation</td>
<td>Determines the type of immunoglobulin heavy chain and light chain once a band of restricted mobility is identified.</td>
</tr>
<tr>
<td>Free light chains</td>
<td>Measures the amount of free light chains in serum. SPEP only measures level of intact immunoglobulin in the blood.</td>
</tr>
<tr>
<td>Fluorescence in situ hybridization (FISH)</td>
<td>Use of genetically engineered probes to detect specific deoxyribonucleic acid (DNA) sequences.</td>
</tr>
</tbody>
</table>
# Laboratory Evaluation

<table>
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<th>Type of Data</th>
</tr>
</thead>
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</table>
# mSMART

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Standard Risk</th>
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</thead>
<tbody>
<tr>
<td>• Del 17p</td>
<td>• t(4;14) [FGFR3/MMSET]</td>
<td>• Trisomies</td>
</tr>
<tr>
<td>• t(14;16) [CMAF]</td>
<td>• 1q gain</td>
<td>• t(11;14) [CCND1]</td>
</tr>
<tr>
<td>• t(14;20) [MAFB]</td>
<td>• High PC S-phase</td>
<td>• t(6;14) [CCND3]</td>
</tr>
<tr>
<td>• Genomic Expression Profile (GEP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• High risk signature</td>
<td></td>
<td></td>
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</tbody>
</table>

## Revised International Staging System

<table>
<thead>
<tr>
<th>rISS 1</th>
<th>β-microglobulin &lt; 3.5 mg/dL, serum albumin ≥ 3.5 g/dL, LDH &lt; ULN, no high risk cytogenetic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>rISS 2</td>
<td>Not rISS stage 1 or 3</td>
</tr>
<tr>
<td>rISS 3</td>
<td>β-microglobulin ≥ 5.5 mg/dL, LDH &gt; ULN – or – presence of del(17p), and/or t(4;14), and/or t(14;16)</td>
</tr>
</tbody>
</table>

ULN= upper limit of normal

# Response Criteria

<table>
<thead>
<tr>
<th>Response</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>sCR (stringent complete response)</td>
<td>In addition to CR criteria, normal FLC ratio and disappearance of plasma cell clones in the bone marrow by immunohistochemistry or fluorescence</td>
</tr>
<tr>
<td>CR (complete response)</td>
<td>Negative M-protein by immunofixation, disappearance of any plasmacytoma and &lt; 5% plasma cells in the bone marrow</td>
</tr>
<tr>
<td>VGPR (very good partial response)</td>
<td>Serum and urine M-protein detectable by immunofixation but not electrophoresis</td>
</tr>
<tr>
<td>PR (partial response)</td>
<td>≥ 50% reduction in serum M-protein; ≥ 90% reduction in urine M-protein; ≥ 50% reduction in FLC ratio in those without M-protein; in addition if plasmacytoma present ≥ 50% reduction in size</td>
</tr>
<tr>
<td>PD (progressive disease)</td>
<td>Increase ≥ 25% in serum or urine M-protein; increased FLC ratio in those without detectable M-protein; ≥ 10% plasma cells in the bone marrow; new or worsening bone lesions or plasmacytoma; hypercalcemia attributed to myeloma</td>
</tr>
<tr>
<td>Relapse</td>
<td>Direct indicator of increasing disease or end organ involvement</td>
</tr>
</tbody>
</table>

KH is diagnosed with ISS 1, IgA kappa symptomatic multiple myeloma. She is 46 years old with end organ involvement including bone lesions and anemia. Scr 0.98, total bilirubin 0.9, calcium 10.5. Which of the following is the best initial treatment for KH?

- **A** elotuzumab, lenalidomide and dexamethasone
- **B** lenalidomide, bortezomib and dexamethasone (RVD)
- **C** bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (VDT-PACE)
- **D** daratumumab monotherapy plus zoledronic acid
Question 6

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Active Therapies in Multiple Myeloma

**Historical Standards**
- Corticosteroids
- Alkylating agents
- Interferon
- Anthracyclines

**Novel Agents - Front Line**
- Bortezomib
- Thalidomide
- Lenalidomide

**Novel Agents - Second Line**
- Carfilzomib
- Pomalidomide
- Panobinostat

**2016 New Drugs**
- Ixazomib
- Elotuzumab
- Daratumumab
Initial Treatment of Newly Diagnosed Multiple Myeloma

- Historically, treatment for myeloma consisted of melphalan plus prednisone (MP)
- Aggressive combination chemotherapy did not demonstrate differences in two year survival compared with MP
  - MP: 57.5% (two year survival), 45.7 (median survival, months)
  - Combination chemotherapy: 55.5% (two year survival), 50.7 (median survival, months)
- High dose dexamethasone, autologous transplantation, and the introduction of novel agents improved outcomes in myeloma patients
- Triplet combinations demonstrate better efficacy than doublet combinations but with added toxicity

### Preferred Induction Regimens for Newly Diagnosed MM: Patients eligible for transplant

<table>
<thead>
<tr>
<th>Study*</th>
<th>Treatment</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harousseau JL, et al.</td>
<td>Bortezomib + Dexamethasone</td>
<td>78.5%</td>
<td>36 months</td>
</tr>
<tr>
<td>Sonneveld P, et al.</td>
<td>Bortezomib + Doxorubicin + Dexamethasone</td>
<td>78%</td>
<td>35 months</td>
</tr>
<tr>
<td>Cavo M, et al. Rosinol L, et al.</td>
<td>Bortezomib + Thalidomide + Dexamethasone</td>
<td>93.2%</td>
<td>68% at 3 years 56.2 months</td>
</tr>
<tr>
<td>Richardson PG, et al. Roussel M, et al. Kumar S, et al.</td>
<td>Bortezomib + Lenalidomide + Dexamethasone</td>
<td>100% 93.5% 85%</td>
<td>75% at 18 months 77% at 3 years 83% at 1 year</td>
</tr>
<tr>
<td>Reeder, et al. Kumar S, et al.</td>
<td>Cyclophosphamide + Bortezomib + Dexamethasone</td>
<td>88% 75%</td>
<td>42% at 5 years 93% at 1 year</td>
</tr>
</tbody>
</table>

ORR = overall response rate, PFS = progression free survival

*For full bibliographic citations see last slide*
## Preferred Induction Regimens for Newly Diagnosed MM: Patients ineligible for transplant

<table>
<thead>
<tr>
<th>Study*</th>
<th>Treatment</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>76%</td>
<td>27.5 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>62%</td>
<td>24.1 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>66%</td>
<td>34% at 2 years</td>
</tr>
<tr>
<td>Palumbo A, et al.</td>
<td>Melphalan + prednisone + lenalidomide followed by lenalidomide maintenance</td>
<td>77%</td>
<td>31 months</td>
</tr>
<tr>
<td>San Miguel JF, et al.</td>
<td>Melphalan + prednisone + bortezomib</td>
<td>71%</td>
<td>19.9 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(duration of response)</td>
</tr>
<tr>
<td>Benboubker L, et al.</td>
<td>Lenalidomide + low dose dexamethasone (continuous)</td>
<td>75%</td>
<td>25.5 months</td>
</tr>
</tbody>
</table>

ORR overall response rate, PFS progression free survival

*For full bibliographic citations see last slide*
Preferred Induction Regimens for Newly Diagnosed MM: Patients ineligible for transplant

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<tr>
<th>Study*</th>
<th>Treatment</th>
<th>ORR</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Niesvizky, et al.</td>
<td>Bortezomib + dexamethasone</td>
<td>73%</td>
<td>No difference</td>
</tr>
<tr>
<td>Richardson P, et al.</td>
<td>Bortezomib + lenalidomide + dexamethasone</td>
<td>100%</td>
<td>75% at 18 months</td>
</tr>
<tr>
<td>Kumar S, et al.</td>
<td>Cyclophosphamide + bortezomib + dexamethasone</td>
<td>88%</td>
<td>42% at 5 years</td>
</tr>
</tbody>
</table>

ORR overall response rate, PFS progression free survival

*For full bibliographic citations see last slide*
Patient Case

KH begins treatment with lenalidomide, bortezomib and dexamethasone, 28 day cycles. After her second cycle, you learn she is having difficulty with transportation. KH would like to know if there is an all oral regimen that she can transition to for treatment of her multiple myeloma.
Ixazomib: First and Only Oral Proteasome Inhibitor

- Early clinical studies demonstrated ixazomib well-tolerated and active in multiple myeloma
- Phase 1 study established weekly dosing for ixazomib
- Population pharmacokinetic analysis determined that a change from body surface area (BSA) based dosing to fixed dosing was feasible
- On November 15, 2015 ixazomib was FDA-approved based on the results of the TOURMALINE-MM1 trial.

TOURMALINE-MM1

N=722
- Adult patients
- relapsed and/or refractory multiple myeloma
- measureable disease
- ECOG 0-2
- 1-3 prior lines of therapy

N=360
Ixazomib 4mg Days 1,8,15
Lenalidomide 25mg Days 1-21
Dexamethasone 40mg Days 1,8,15,22

Primary Endpoint: PFS

N=362
Placebo Days 1,8,15
Lenalidomide 25mg Days 1-21
Dexamethasone 40mg Days 1,8,15,22

Secondary Endpoints: OS and OS with 17p deletion

ECOG eastern cooperative oncology group, OS overall survival, PFS progression free survival

TOURMALINE-MM1

• Progression Free Survival (PFS) was significantly longer by 40% with ixazomib as triplet therapy
  – 20.6 versus 14.7 months for ixazomib and placebo, respectively
  – Hazard ratio for disease progression or death 0.74 (95% confidence interval 0.59-0.94; P=0.01)
• PFS benefit held consistently for all pre-specified patient subgroups: high risk cytogenetics, International staging system (ISS) stage III, >75 years of age, 2-3 prior therapies
• Overall response rates 78.3% and 71.5% in the ixazomib and placebo group, respectively (P = 0.04)
• Median overall survival not yet reached

TOURMALINE-MM1

• Median number of cycles were 17 and 15 in the ixazomib and placebo group, respectively (range for ixazomib 1-34 cycles)

• Thromboprophylaxis according to American Society of Clinical Oncologists or institutional standard was required
  – Venous thromboembolism (VTE) occurred in 8% versus 11% of ixazomib and placebo, respectively

• Gastrointestinal events and rash were more common with ixazomib occurring mostly during cycles 1-3 and low grade

• Peripheral neuropathy was 27% and 22% in the ixazomib and placebo groups, respectively

Is Ixazomib Use Safe in Severe Renal Impairment or End Stage Renal Disease (ESRD)?

- Pharmacokinetic evaluation of single dose ixazomib in patients with normal (crcl $\geq$90ml/min), impaired (crcl $<30$ml/min) or end stage renal disease requiring hemodialysis
- Evaluated after a single 3mg dose of ixazomib
- Highly protein bound (99%) in all groups
- Systemic exposures were higher with renal dysfunction (38% and 39% in impaired and ESRD, respectively)
- Grade 3 and 4 adverse events were more frequent in the renally impaired and ESRD groups versus the normal groups as were serious adverse events

Ixazomib Summary

• Ixazomib in combination with lenalidomide and dexamethasone represents the first all oral triplet regimen for multiple myeloma. It demonstrates efficacy and is well tolerated

• Ixazomib are gelatin capsules and should not be refrigerated but does need to be stored at temperatures that do not exceed 86 degrees Fahrenheit or are freezing
  – Manufacturer recommends to avoid shipping ixazomib on ice and to use corrugated cartons for specialty pharmacy shipping

• Ixazomib should be taken on an empty stomach

• Safety of use of ixazomib in patients with creatinine clearance <30ml/min remains unclear

• Currently supported in the relapsed and/or refractory setting and being evaluated for use in maintenance and front line setting
Question 7

KH achieved a very good partial response with ixazomib, lenalidomide and dexamethasone and went on to consolidation with autologous stem cell transplantation. KH declined maintenance therapy. Two years later her immunofixation tests detect M-protein and her FLC ratio increases to 5.01 mg/dL. Which of the following therapies would be appropriate for KH’s relapsed disease?

A. carfilzomib, pomalidomide and dexamethasone
B. lenalidomide, dexamethasone
C. bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (VDT-PACE)
D. elotuzumab, lenalidomide and dexamethasone
Question 7

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Elotuzumab Mechanism of Action

- Elotuzumab binds SLAMF7
- Couple with EAT-2
- Activation of natural killer cell
- Antibody dependent cell mediated cytotoxicity

- Elotuzumab tags myeloma cell via SLAMF7
- No EAT-2 coupling → no proliferation

Elotuzumab package insert
ELOQUENT-2

• Adults with multiple myeloma and measurable disease who had received 1-3 prior therapies

<table>
<thead>
<tr>
<th>Treatment cohort (n=321)</th>
<th>Active control cohort (n=325)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elotuzumab 10mg/kg IV on days 1,8,15,22 for cycles 1 and 2. For cycles 3 and beyond on days 1,15</td>
<td>• Lenalidomide 25mg PO on days 1-21</td>
</tr>
<tr>
<td>• Lenalidomide 25mg PO on days 1-21</td>
<td>• Dexamethasone 40mg PO on days 1,8,15,22</td>
</tr>
<tr>
<td>• Dexamethasone 40mg PO weekly (on the weeks without elotuzumab) and 8mg IV plus 28mg PO weekly with elotuzumab</td>
<td></td>
</tr>
</tbody>
</table>
ELOQUENT-2

• Co-primary endpoints were PFS and overall response rates (ORR)
  – Median PFS for elotuzumab was 19.4 months and 14.9 months for control arm. Hazard ratio for disease progression and death of 0.7 (95% CI, 0.57-0.85; P<0.001)
  – ORR were 79% for elotuzumab and 66% for control arm (odds ratio for the elotuzumab group versus the control group, 1.9; 95% CI, 1.4-2.8; P<0.001)

• No notable differences in pain severity from baseline and quality of life (per EORTC QLQ-C30) between the two groups

ELOQUENT-2

- More patients experienced grade 3-4 lymphocytopenia in the elotuzumab arm (77% versus 49%)
- Rate of herpes zoster infection was higher in the elotuzumab group when compared with control (incidence per 100 patient years, 4.1 versus 2.2)
- Infusion reactions (e.g. pyrexia, chills, hypertension) occurred in 33 patients with most occurring with the first dose and no grade 4 or 5 reaction

Elotuzumab Summary

- Elotuzumab is a well tolerated triplet regimen and demonstrates improved ORR and PFS when used in combination
  - Lacks single agent activity
- Patients should receive premedications for elotuzumab, herpes zoster prophylaxis and standard thromboprophylaxis
- Dexamethasone dosing is complicated and care should be taken with regard to patient adherence
- Key role for pharmacists is assistance with adherence and synchronization of oral therapies with parenteral cycles
Patient Case

KH tolerated elotuzumab, lenalidomide and dexamethasone. Unfortunately, her myeloma progressed after 8 cycles and her therapy was changed to carfilzomib, pomalidomide and dexamethasone. After four cycles of this therapy, she developed a soft tissue plasmacytoma in the right flank.
Question 8

Which of the following is the best therapeutic plan for KH?

A. Continue current therapy (e.g. carfilzomib, pomalidomide, dexamethasone)

B. Bortezomib, doxorubicin, thalidomide, cisplatin, dexamethasone, cyclophosphamide, etoposide (VDT-PACE)

C. Daratumumab monotherapy

D. Pomalidomide and dexamethasone
Question 8

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Open poll in your web browser
Daratumumab

- Humanized monoclonal antibody that targets CD38, a transmembrane protein highly expressed on malignant plasma cells
- Binding of daratumumab to CD38 triggers complement activation and complement dependent cytotoxicity
- Daratumumab also triggers antibody dependent cellular cytotoxicity (ADCC)
  - Modulation of enzymatic activation
  - Apoptosis after cross linking

DARA-GEN501

- Phase 1-2, open label, multicentered trial of dose-escalation and dose expansion
- Primary outcome was safety with secondary efficacy outcomes that included pharmacokinetics, objective response, relative reduction in M-protein/FLC, time to disease progression, duration of response, PFS and overall survival (OS)
- With higher doses of daratumumab, a new assay was used to measure disease response

DARA-GEN501

• Patients were adults, with ECOG ≤2 and measureable disease
• Part 1 dose escalation up to 24mg/kg, part 2 is dose expansion with cohorts receiving 8mg/kg and cohorts receiving 16mg/kg
• The primary endpoint was safety with secondary endpoints that included pharmacokinetic analysis, reduction in M-protein, light chains, duration of response, time to progression, PFS, OS

DARA-GEN501

Part 1: Dose-Escalation Study
- No maximum tolerated dose was identified
- 33% of patients had a partial response

Part 2: Dose-Expansion Study

<table>
<thead>
<tr>
<th>Cohort</th>
<th>8 mg/kg</th>
<th>16 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in M-Protein</td>
<td>15% of patients</td>
<td>46% of patients</td>
</tr>
<tr>
<td>Overall response rate</td>
<td>10%</td>
<td>36%</td>
</tr>
<tr>
<td>PFS</td>
<td>2.4 months</td>
<td>5.6 months</td>
</tr>
<tr>
<td>Median time to first response</td>
<td>0.9 months</td>
<td>Not reached</td>
</tr>
<tr>
<td>Median duration of response</td>
<td>6.9 months</td>
<td>65% of responders progression-free at 12 months</td>
</tr>
</tbody>
</table>

SIRIUS

• Phase 2, two part, open label, multicenter study
• ECOG ≤ 2
• Included adult patients with secretory myeloma and evidence of disease progression within 60 days of the last dose of the most recent regimen
  – Responded to one prior regimen
  – Received an alkylating agent
  – Received at least 3 prior regimens that included a proteasome inhibitor and immunomodulating drug
  – Double refractory disease to most recent proteasome inhibitor and immunomodulating drug

SIRIUS

- Phase 1 evaluated 8mg/kg and 16mg/kg doses. The 8mg/kg cohort did not meet criteria for expansion (dose likely did not meet trough threshold for saturation) but 16mg/kg went on to phase 2 dose expansion

<table>
<thead>
<tr>
<th>Daratumumab 16mg/kg (n=106)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>31 (29.2%, 20.8-38.9)</td>
</tr>
<tr>
<td>Clinical benefit rate</td>
<td>36 (34%, 25-43.8)</td>
</tr>
<tr>
<td>≥ Very good partial response</td>
<td>13 (12.3%, 6.7-20.1)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>46 (43.4%, 33.8-53.4)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>18 (17%, 10.4-25.5)</td>
</tr>
</tbody>
</table>

Daratumumab Improves OS

- Combined analysis of the DARA-GEN501 and SIRIUS trials demonstrates overall survival benefit with daratumumab monotherapy in heavily pretreated patients
- ORR 31%
- Median OS 19.9 months
  - Median OS has not been reached in responders

Daratumumab in Combination

• Pretreatment with immunomodulation has demonstrated enhanced antibody dependent cellular cytotoxicity in multiple myeloma cells through activation of natural killer cells.
  – Allows for synergistic activity to take place between the immunomodulatory drug and daratumumab
  – Immunomodulation to activate T and natural killer cells coupled with daratumumab-induced antibody dependent cellular cytotoxicity

• Synergistic activity may overcome drug resistance mechanisms of myeloma cells

Daratumumab in Combination

- Daratumumab + Pomalidomide + Dexamethasone

<table>
<thead>
<tr>
<th></th>
<th>ORR</th>
<th>VGP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daratumumab monotherapy</td>
<td>36%</td>
<td>13%</td>
</tr>
<tr>
<td>Daratumumab + pomalidomide + dexamethasone</td>
<td>71%</td>
<td>43%</td>
</tr>
</tbody>
</table>


Daratumumab Summary

• Daratumumab represents a viable treatment option for patients with disease refractory to both proteasome inhibitors and immunomodulatory agents

• Daratumumab does interfere with blood typing and a type and screen should be obtained prior to therapy

• Cycle one day one infusions may require a lengthy infusion time

• Patients should receive prophylaxis for herpes zoster infection
  – Prophylaxis for infusion-related reactions
  – Premedication with montelukast?
Future Directions

• Daratumumab is currently being studied in combination with various multiple myeloma backbone regimens

• Specialty pipeline includes other oral proteasome inhibitors and histone deacetylase drugs
Supportive Care

• All patients receiving an immunomodulating agent in combination with corticosteroids should receive anticoagulation prophylaxis
  – Aspirin 81-325mg daily if no additional risk factors
  – If risk factors present enoxaparin 40mg SC daily

• Herpes zoster prophylaxis should be used in patients receiving elotuzumab and daratumumab

• Patients receiving daratumumab may consider a medic alert bracelet in case a blood transfusion is required during treatment
Conclusions

• Ixazomib allows for the first all oral triplet multiple myeloma regimen
• Elotuzumab does not demonstrate single agent activity but is effective in combination with lenalidomide and dexamethasone
• Daratumumab demonstrates single agent activity in heavily pretreated and dual refractory patients and early studies suggest an overall survival benefit
Full Reference Citations for Preferred Regimens in Newly Diagnosed MM

Transplant candidates

Non-transplant candidates
Questions?