BCOP Clinical Sessions-Multiple Myeloma and Pediatric CINV II

Activity Number: 0217-9999-16-145-L01-P, 2.0 Hours of CPE Credit; Activity Type: An Application-Based Activity

Wednesday October 26, 2016

8:00 a.m. to 10:00 a.m.
Great Hall 6

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 ACCP and the American Society of Health-System Pharmacists (ASHP). Part II will be presented on Wednesday, October 26, from 8:00 a.m. to 10:00 a.m. During the Oncology Pharmacy Specialty Sessions, instructions for accessing the BCOP recertification posttests will be provided (two posttests - one for each session). The deadline to submit posttests for these sessions will be March 1, 2017. Note: This session will be recorded and will be available for future playback.

Moderator: Jill Bates, Pharm.D., M.S., BCOP
Assistant Professor of Clinical Education; Clinical Pharmacy Specialist in Malignant Hematology, University of North Carolina, Chapel Hill, North Carolina

Agenda

8:00 a.m.	Evolving Treatment Strategies for Multiple Myeloma *Jill Bates, Pharm.D., M.S., BCOP* Assistant Professor of Clinical Education; Clinical Pharmacy Specialist in Malignant Hematology, University of North Carolina, Chapel Hill, North Carolina
9:00 a.m.	Management of Pediatric CINV: A Complex Case *Jennifer L. Thackray, Pharm.D., BCPS, BCPPS* Pediatric Oncology Clinical Pharmacy Specialist, Memorial Sloan Kettering Cancer Center, New York, New York

Conflict of Interest Disclosures

Jill Bates: no conflicts to disclose
Catherine Lee: no conflicts to disclose.
Erika Mora: no conflicts to disclose.
Polly Kintzel: no conflicts to disclose.
Jennifer L. Thackray: no conflicts to disclose

External Reviewers

ACCP/ASHP would like to thank the following reviewers for this program:

Catherine S. Lee, Pharm.D., BCPS, BCOP
Clinical Pharmacist, Hematology/Oncology
Wake Forest Baptist Medical Center
Kernersville, North Carolina

Erika Mora, Pharm.D., BCOP
Clinical Pharmacist Specialist
Pediatric Hematology/Oncology
University of Michigan Hospital and Health Systems
C.S. Mott Children's Hospital
Adjunct Clinical Instructor
University of Michigan College of Pharmacy
Ann Arbor, Michigan

Polly E Kintzel, Pharm.D., BCOP, BCPS
Clinical Pharmacy Lead for Adult BMT and Oncology
Spectrum Health Grand Rapids
Grand Rapids, Michigan

Learning Objectives

1. Examine prognostic implications and outline patient-specific treatment for multiple myeloma.
2. Discuss pertinent literature related to daratumumab, elotuzumab and ixazomib.
3. Illustrate current role in therapy of novel agents to treat multiple myeloma.
4. Define the phases of chemotherapy-induced nausea and vomiting (CINV) and recognize the risk factors for CINV in a pediatric patient.
5. Analyze the safety and efficacy of aprepitant and palonosetron in pediatric patients.
6. Develop a plan for prevention and treatment of each phase of CINV.
7. Modify an antiemetic regimen for a pediatric patient with breakthrough CINV.

Self-Assessment Questions

Self-assessment questions are available online at www.accp.com/am

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

accp American College of Clinical Pharmacy

ashp Certification Resources

Learning Objectives

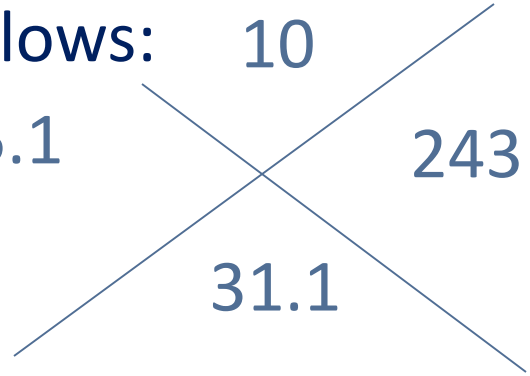
- Examine prognostic implications and outline patient-specific treatment for multiple myeloma
- Discuss pertinent literature related to ixazomib, elotuzumab and daratumumab
- Illustrate the current roles in therapy of novel agents to treat multiple myeloma

Faculty Disclosures

- Nothing to disclose.

Patient Case

KH is a 59 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

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 ratio 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

Audience Response

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

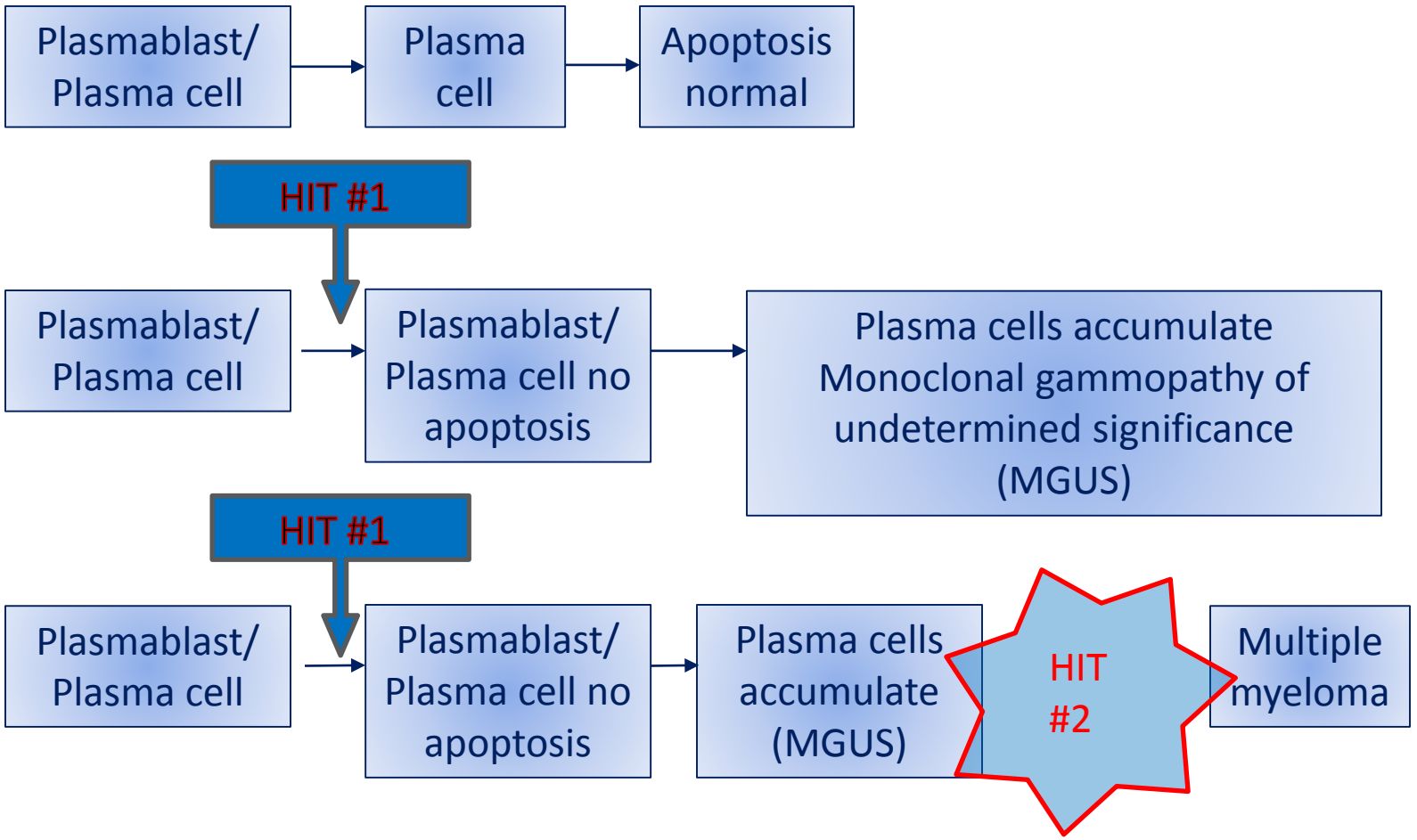
ISS= International Staging System
AL= amyloid light chain

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

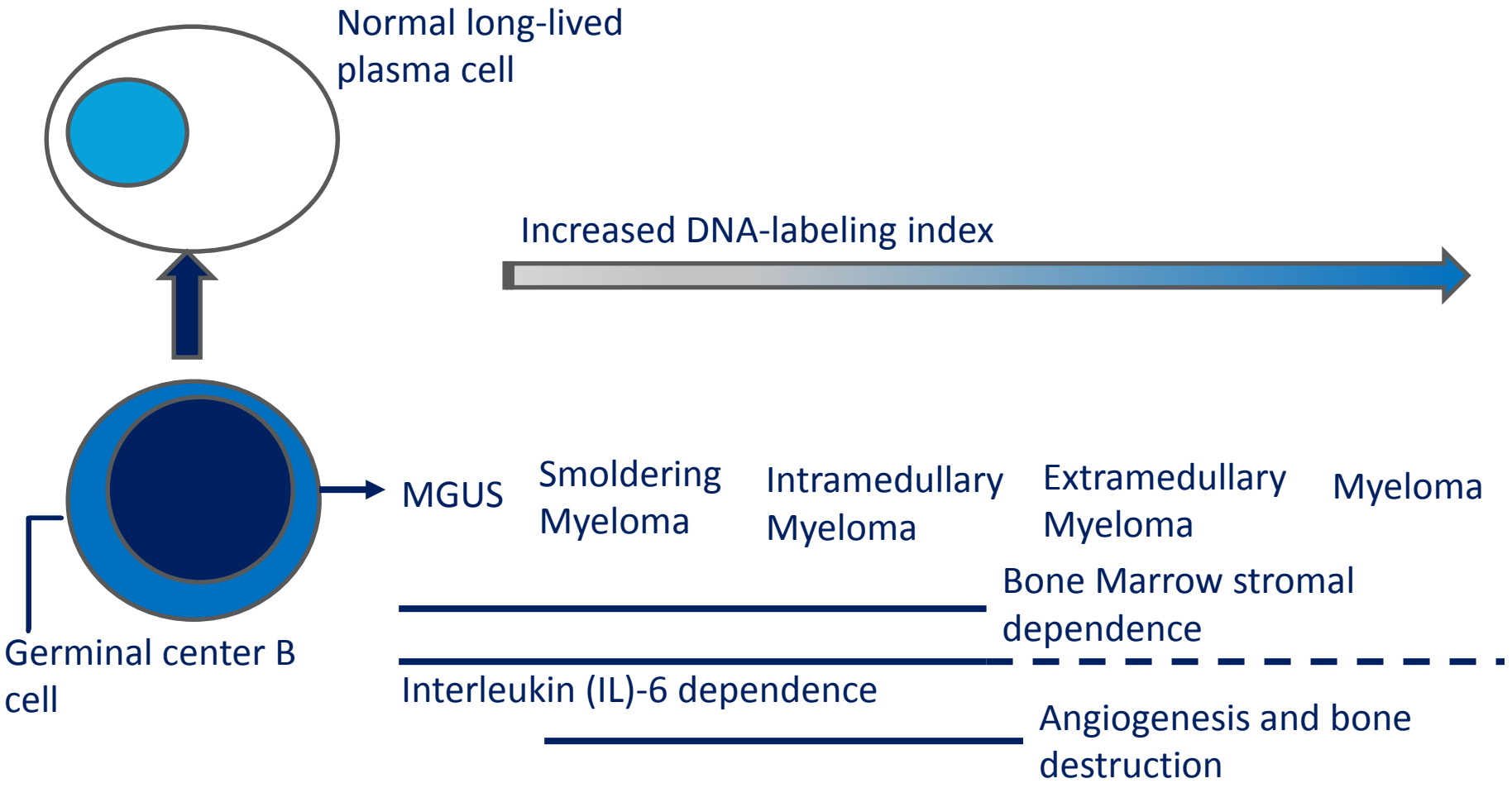
Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Altekruse SF, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2013, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016.

The Double Hit Hypothesis in MM



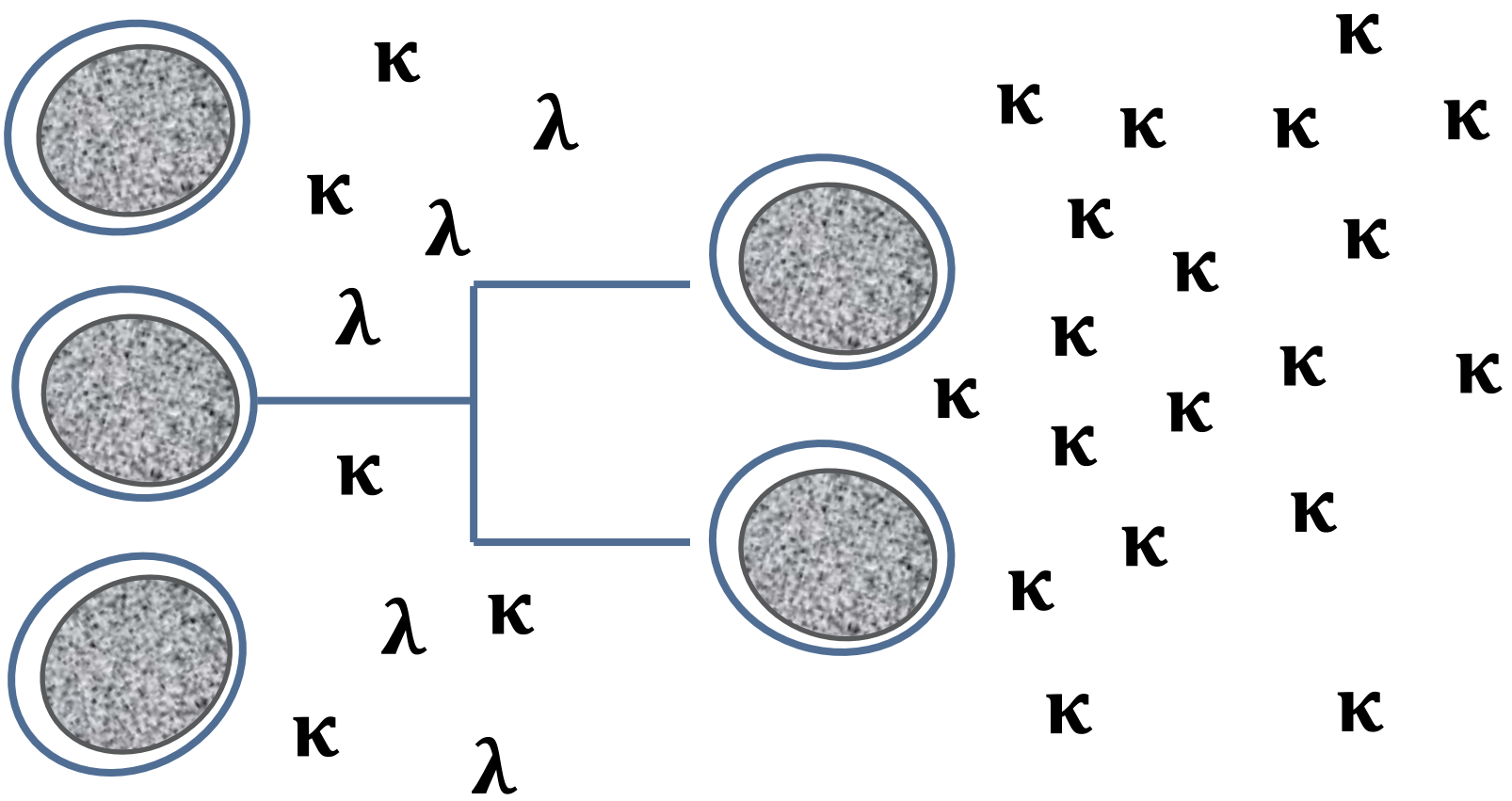
Hallek, et al. Blood 1998;91:3-21.
Kuehl WM, et al. Nature Rev Cancer. 2002;2:175-87.

Spectrum of Disease Progression



Hallek, et al. Blood 1998;91:3-21.
Kuehl WM, et al. Nature Rev Cancer. 2002;2:175-87.

Monoclonality



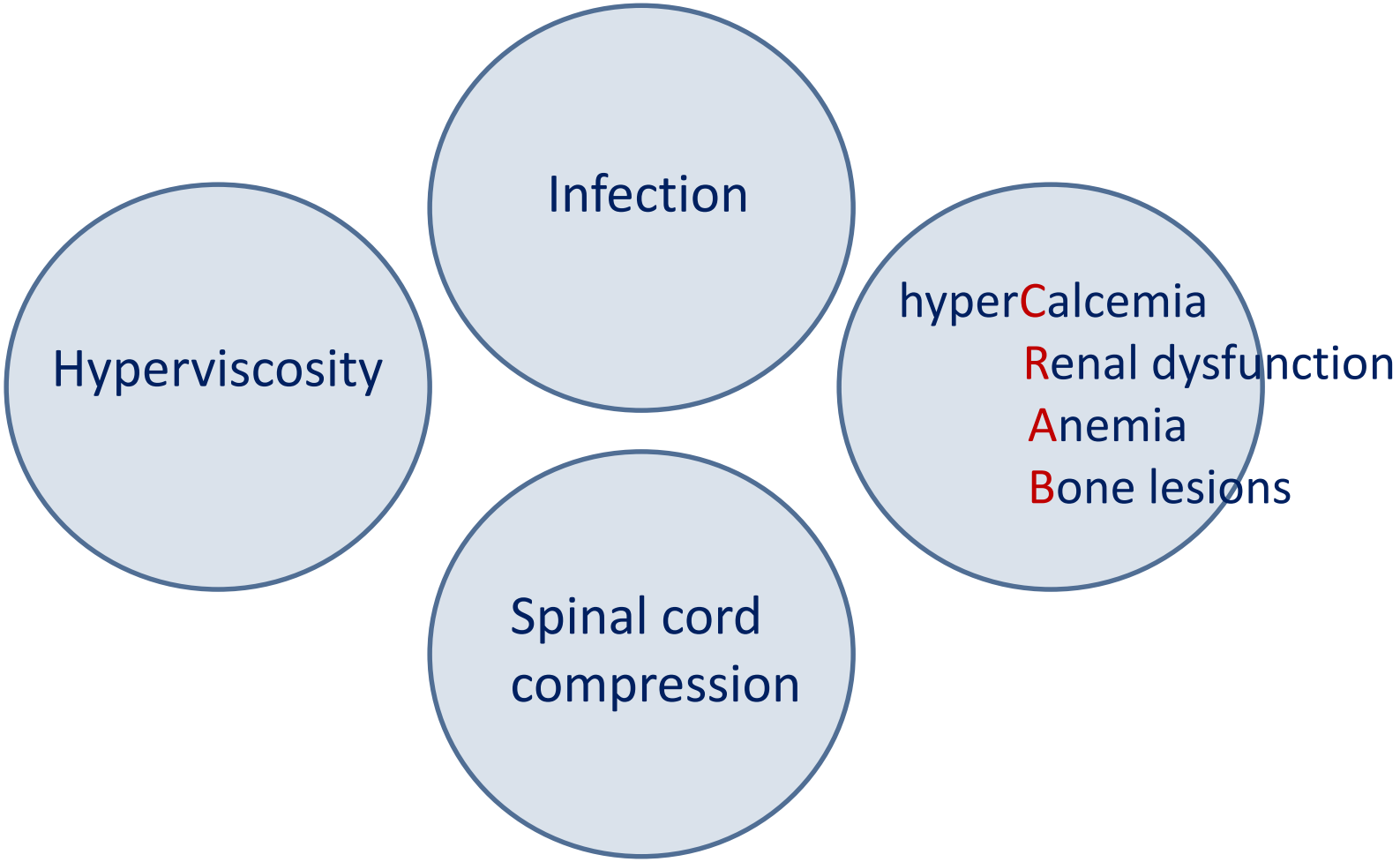
https://www.med-ed.virginia.edu/courses/path/innes/wcd/immunointro.cfm [accessed 7/30/16].

Three Definitions of "Multiple Myeloma"

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

Kyle RA, Rajkumar SV. Leukemia 2009;23:3-9.

Myeloma-related Organ or Tissue Impairment



Bird JM, et al. Br J Haem. 2011;154:32-75.

Laboratory Evaluation

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

mSMART

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

Kumar SK, et al. Mayo Clin Proc 2009;84:1095-1110.

Revised International Staging System

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

ULN= upper limit of normal

Palumbo A, et al. J Clin Oncol 2015;33:2863-9.

Response Criteria

Response	Criteria
sCR (stringent complete response)	In addition to CR criteria, normal FLC ratio and disappearance of plasma cell clones in the bone marrow by immunohistochemistry or fluorescence
CR (complete response)	Negative M-protein by immunofixation, disappearance of any plasmacytoma and < 5% plasma cells in the bone marrow
VGPR (very good partial response)	Serum and urine M-protein detectable by immunofixation but not electrophoresis
PR (partial response)	≥ 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
PD (progressive disease)	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
Relapse	Direct indicator of increasing disease or end organ involvement

Durie BGM, *et al.* Leukemia 2006;20:1467-73.

Audience Response

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?

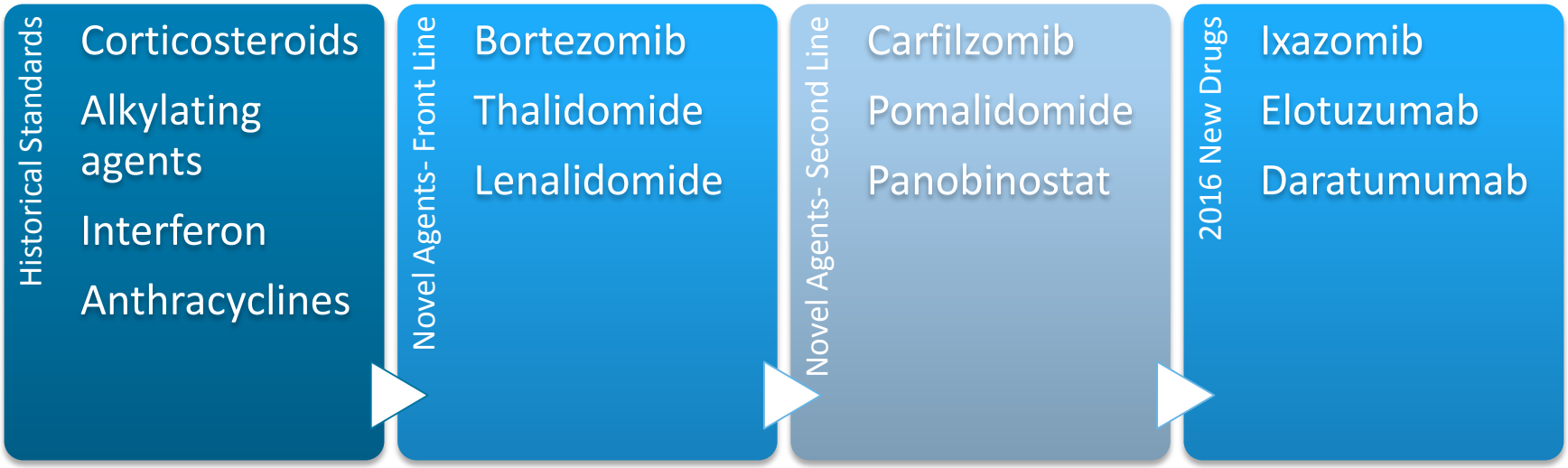
A. elotuzumab, lenalidomide and dexamethasone
B. lenalidomide, bortezomib and dexamethasone (RVD)
C. bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, etoposide (VDT-PACE)
D. daratumumab monotherapy plus zoledronic acid

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

Gregory WM, Richards MA, Malpas JS. J Clin Oncol 1992;10:334-42.

Active Therapies in Multiple Myeloma



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

Study*	Treatment	ORR	PFS
Harousseau JL, et al.	Bortezomib + Dexamethasone	78.5%	36 months
Sonneveld P, et al.	Bortezomib + Doxorubicin + Dexamethasone	78%	35 months
Cavo M, et al. Rosinol L, et al.	Bortezomib + Thalidomide + Dexamethasone	93.2% 85%	68% at 3 years 56.2 months
Zonder JA, et al. Gay F, et al.	Lenalidomide + Dexamethasone	Halted 80.3%	Halted 27.4 months
Richardson PG, et al. Roussel M, et al. Kumar S, et al.	Bortezomib + Lenalidomide + Dexamethasone	100% 93.5% 85%	75% at 18months 77% at 3 years 83% at 1 year
Reeder, et al. Kumar S, et al.	Cyclophosphamide + Bortezomib + Dexamethasone	88% 75%	42% at 5 years 93% at 1 year

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

Study*	Treatment	ORR	PFS
Palumbo A, et al. Facon T, et al. Hulin C, et al. Wijermans P, et al.	Melphalan + prednisone + thalidomide	76% 76% 62% 66%	21.8 months 27.5 months 24.1 months 34% at 2 years
Palumbo A, et al.	Melphalan + prednisone + lenalidomide followed by lenalidomide maintenance	77%	31 months
San Miguel JF, et al.	Melphalan + prednisone + bortezomib	71%	19.9 months (duration of response)
Benboubker L, et al.	Lenalidomide + low dose dexamethasone (continuous)	75%	25.5 months

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

Study*	Treatment	ORR	PFS
Niesvizky, et al.	Bortezomib + dexamethasone	73%	No difference
Richardson P, et al.	Bortezomib + lenalidomide + dexamethasone	100%	75% at 18 months
Kumar S, et al.	Cyclophosphamide + bortezomib + dexamethasone	88%	42% at 5 years

ORR overall response rate, PFS progression free survival

*For full bibliographic citations see last slide

Patient Case

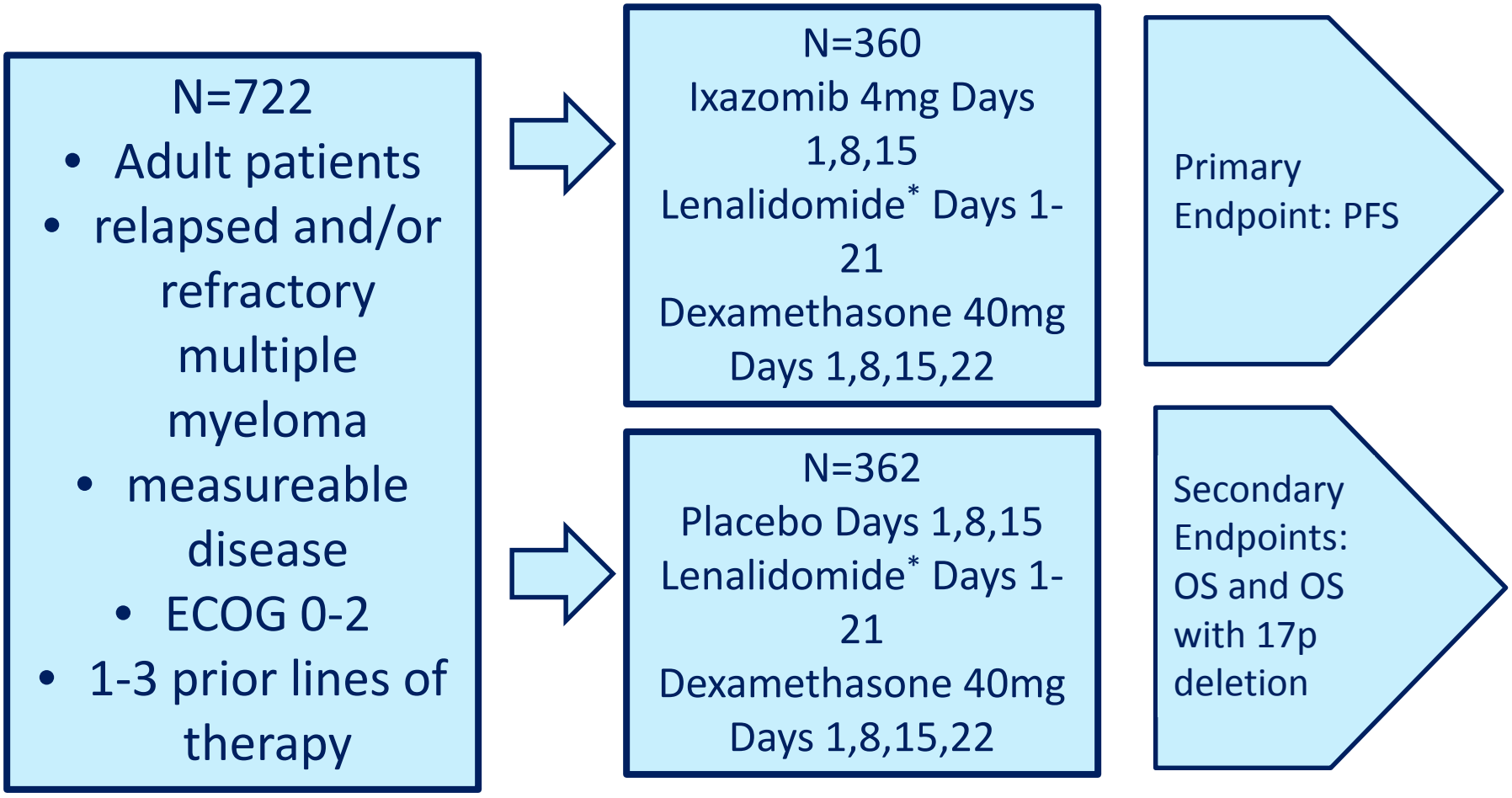
KH begins treatment with lenalidomide, bortezomib and dexamethasone, 28 day cycles. After her second cycle, you learn she is having difficulty with transportation. KH would like to know if there is an all oral regimen that she can transition to for treatment of her multiple myeloma.

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.

Kumar SK, et al. Blood Cancer J. 2105;Aug 14;doi:10.1038/bcj.2015.60.
Kumar SK, et al. Lancet Oncol 2014;15:1503-12.
Gupta N, et al. Br J Clin Pharmacol. 2015;79:789-800.
Kumar SK, et al. Blood. 2014;124:1047-55.

TOURMALINE-MM1



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

Moreau P, et al. N Engl J Med. 2016;374:1621-34.

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

Moreau P, et al. N Engl J Med. 2016;374:1621-34.

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

Moreau P, et al. N Engl J Med. 2016;374:1621-34.

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 ≥90ml/min), impaired (crcl <30ml/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

Gupta N, et al. Br J Haematol. 2016;May 16.doi:10.1111/bjh.14125.

Ixazomib Summary

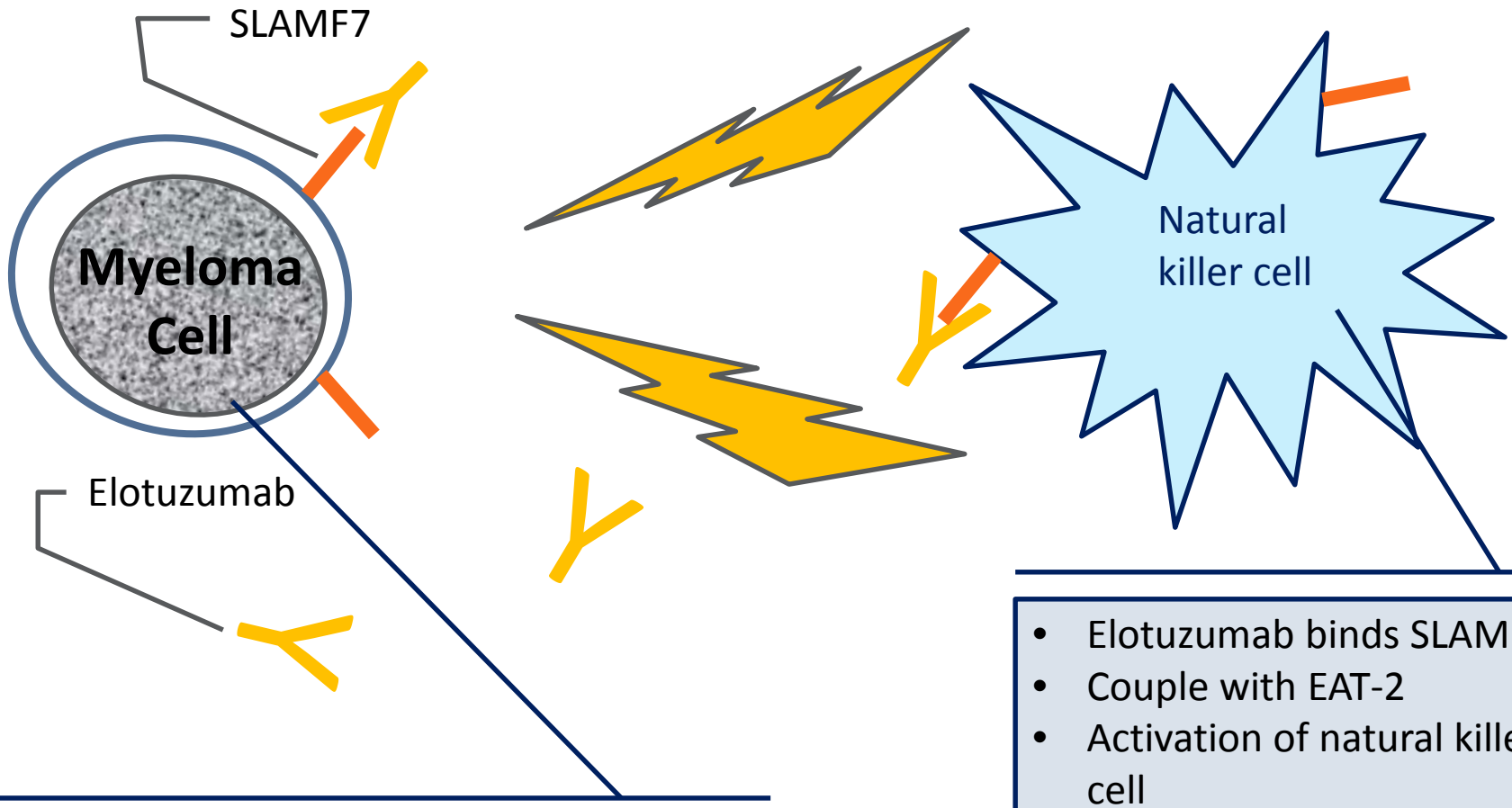
- Ixazomib in combination with lenalidomide and dexamethasone represents the first all oral triplet regimen for multiple myeloma. It demonstrates efficacy and is well tolerated
- Ixazomib are gelatin capsules and should not be refrigerated but does need to be stored at temperatures that do not exceed 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

Audience Response

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

Elotuzumab Mechanism of Action



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

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

Elotuzumab package insert

ELOQUENT-2

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

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

Lonial S, et al. N Engl J Med. 2015;373:621-31.

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

Lonial S, et al. N Engl J Med. 2015;373:621-31.

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

Lonial S, et al. N Engl J Med. 2015;373:621-31.

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.

Audience Response

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

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

Phipps C, et al. Ther Adv Hematol. 2015;6:120-7.

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

Lokhorst, et al. N Engl J Med. 2015;373:1207-19.

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

Lokhorst, et al. N Engl J Med. 2015;373:1207-19.

DARA-GEN501

- Safety events were mild, 71% of patients experienced grade 1 and 2 infusion reactions
- Adverse events were not dose related

Part 1: Dose-Escalation Study

- No maximum tolerated dose was identified
- 33% of patients had a partial response

Part 2: Dose-Expansion Study

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

Lokhorst, et al. N Engl J Med. 2015;373:1207-19.

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

Lonial S, et al. Lancet. 2016;387:1551-60.

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

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

Lonial S, et al. Lancet. 2016;387:1551-60.

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

Myeloma updates. Am Health Drug Benefits. 2016;9:14.

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

Khagi Y, Mark TM. *OncoTargets and therapy.* 2014;7:1095-1100.

Daratumumab in Combination

- Daratumumab + Pomalidomide + Dexamethasone

	ORR	VGPR
Daratumumab monotherapy	36%	13%
Daratumumab + pomalidomide + dexamethasone	71%	43%

Lokhorst, et al. N Engl J Med. 2015;373;1207-19.

Chari A, et al. Open-Label, Multicenter, Phase 1b Study of Daratumumab in Combination with Pomalidomide and Dexamethasone in Patients with at Least 2 Lines of Prior Therapy and Relapsed or Relapsed and Refractory Multiple Myeloma. Paper presented at: American Society of Hematology2015; Orlando, FL

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

- Harousseau JL, et al. J Clin Oncol. 2010;28:4621-9.
- Sonneveld P, et al. J Clin Oncol. 2012;30:2946-55.
- Cavo M, et al. Lancet. 2010;376:2075-85.
- Rosinol L, et al. Blood. 2012;120:1589-96
- Zonder JA, et al. Blood. 2007;110:abstract 77.
- Gay F, et al. Blood 2010;115:1343-50.
- Richardson P, et al. Blood. 2010;116:679-86.
- Roussel M, et al. J Clin Oncol. 2014;32:2712-7.
- Kumar S, et al. Blood. 2012;119:4375-82.
- Reeder, et al. Leukemia. 2009;23:1337-41.

Non-transplant candidates

- Palumbo, et al. Lancet. 2006;367:825-31.
- Palumbo, et al. Blood. 2008;112:3107-14.
- Facon T, et al. Lancet. 2007;370:1209-18.
- Hulin C, et al. J Clin Oncol. 2009;27:3664-70.
- Palumbo A, et al. N Engl J Med. 2012;366:1759-69.
- San Miguel JF, et al. N Engl J Med. 2008;359:906-17.
- Benboubker L, et al. N Engl J Med. 2014;371:906-17.
- Niesvizky, et al. Blood. 2011;118:Abstract 478.
- Richardson P, et al. Blood. 2010;116:679-86.
- Kumar S, et al. Blood. 2012;119:4375-82.

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

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Management of Pediatric Chemotherapy-Induced Nausea and Vomiting: A Complex Case

Jennifer Thackray, PharmD, BCPS, BCPPS

Pediatric Oncology Clinical Pharmacy Specialist

Memorial Sloan Kettering Cancer Center

New York, New York

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Faculty Disclosures

- 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

ARS Question

- 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%

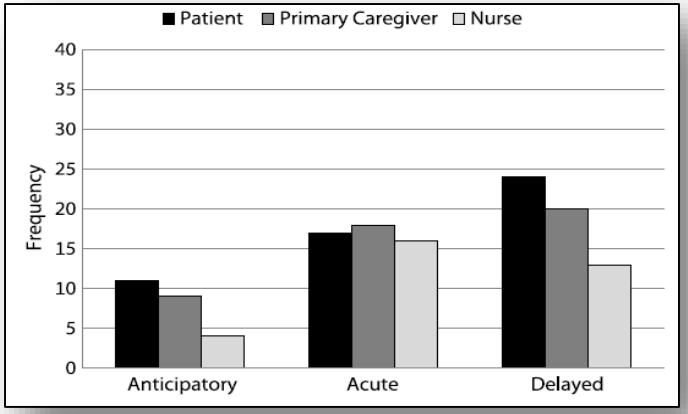
C. 20 – 49%

D. < 20%

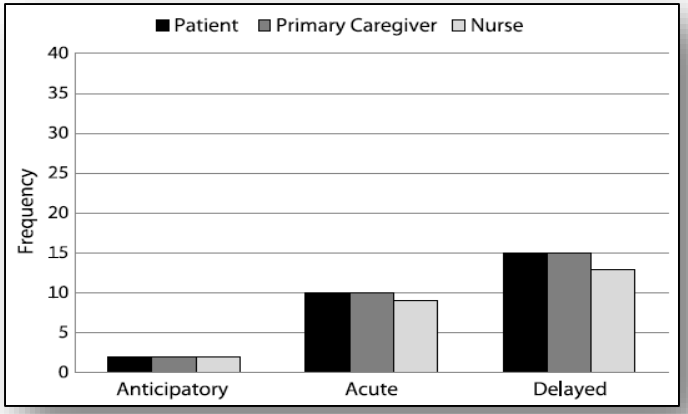
Introduction

- 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

Nausea Frequency (n=40)

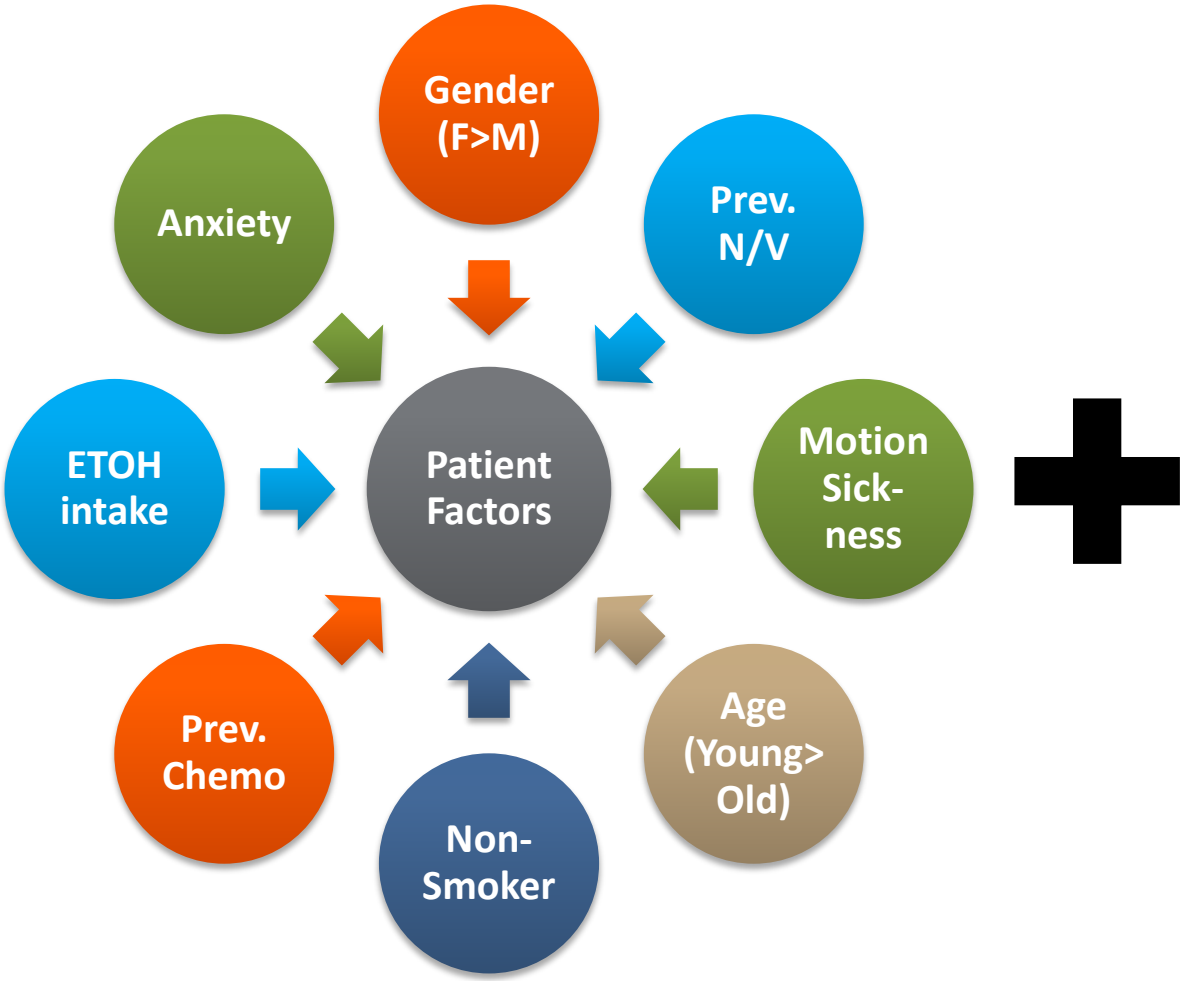


Vomiting Frequency (n=40)



Freedman JL, et al. *Pediatr Blood Cancer.* 2014;61:1798-1805. Kang HJ, et al. *Lancet Oncol.* 2015;16:385-94. Rodgers C, et al. *Cancer Nursing.* 2012;35(3):203-10. Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

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

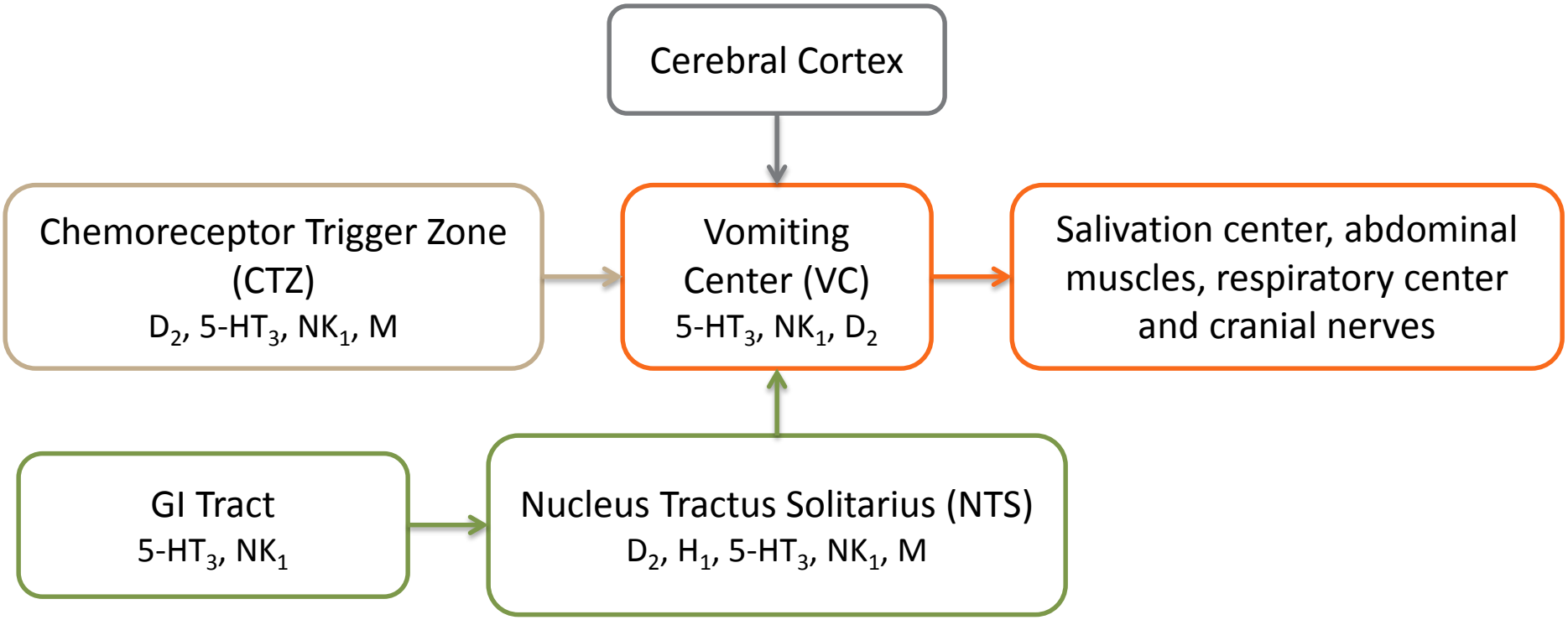
Freedman JL, et al. *Pediatr Blood Cancer.* 2014;61:1798-1805. Kang HJ, et al. *Lancet Oncol.* 2015;16:385-94. Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

Complications

- Physiologic
  - Malnutrition
  - Weight loss
  - Esophageal tears
  - Dehydration
  - Fatigue
- Metabolic
  - Electrolyte imbalances
- Psychological
  - Anxiety
  - Non-adherence
  - Reduced future chemotherapy doses
  - Decreased quality of life

Freedman JL, et al. *Pediatr Blood Cancer.* 2014;61:1798-1805. Kang HJ, et al. *Lancet Oncol.* 2015;16:385-94. Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

Neurotransmitters



D_2: Dopamine 2 receptor
5-HT_3: Serotonin type 3 receptor
NK_1: Neurokinin 1 receptor (Substance P)

H_1: Histamine 1 receptor
M: Muscarinic cholinergic receptor (Acetylcholine)

Navari RM, et al. *N Engl J Med*. 2016;374:1356-67. Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

Current Standard of Care for Prevention of Pediatric CINV

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Phases of CINV

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

$5HT_3RA$
DEXA
D_2RA
OLZ

Delayed
- > 24 hours following completion of chemotherapy
- Mechanism not fully understood
- Substance P/NK_1 receptors

NK_1RA
DEXA
OLZ
PALO?

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

BZD
Music therapy
Acupuncture
Hypnosis

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

H_1RA
D_2RA
OLZ
Patient specific

5-HT_3 RA, Serotonin receptor antagonist; DEXA, dexamethasone; D_2 RA, Dopamine 2 receptor antagonist; OLZ, olanzapine; BZD, benzodiazepine; NK_1 RA, Neurokinin 1 receptor antagonist; PALO, palonosetron; H_1 RA, Histamine 1 receptor antagonist

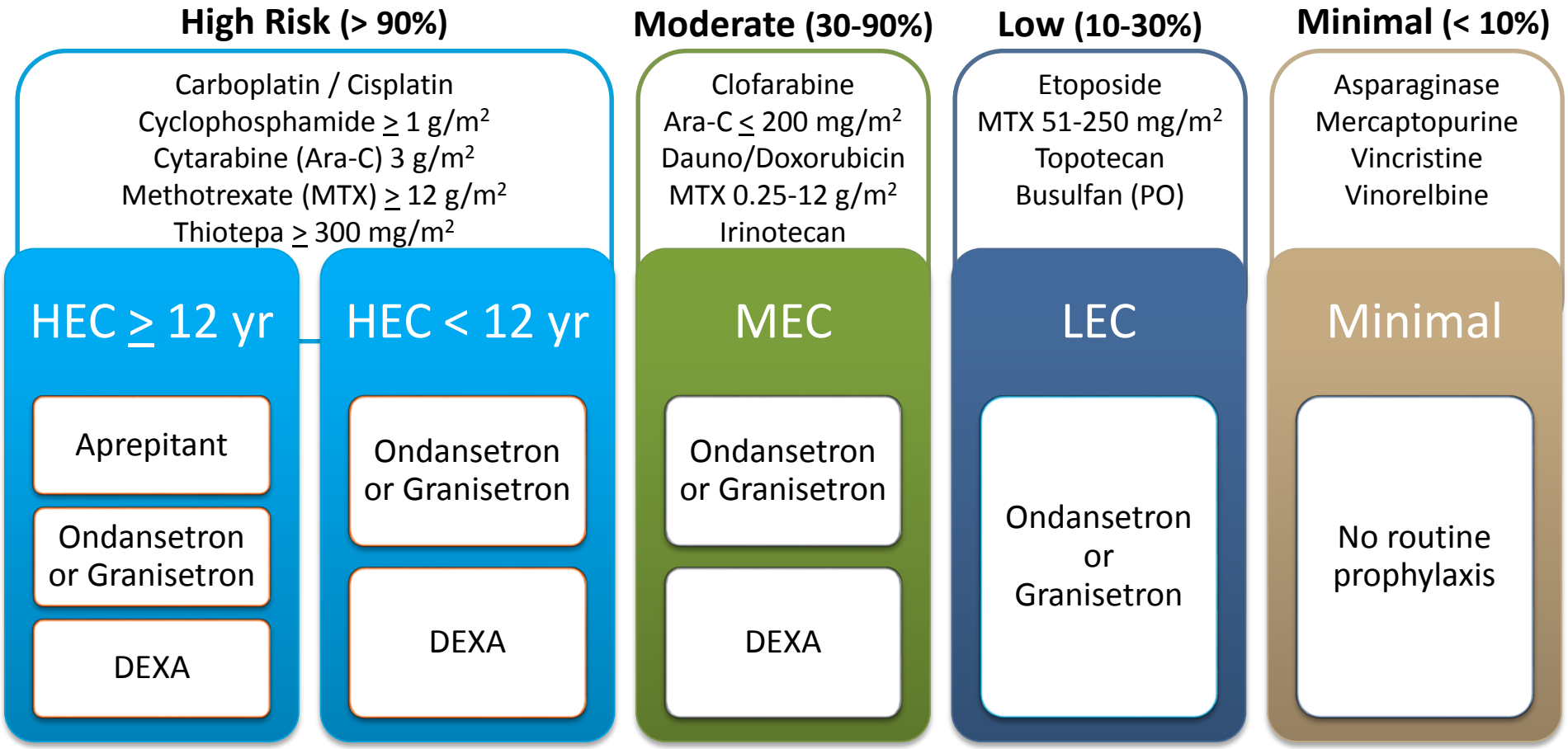
Dupuis LL, et al. *Pediatr Blood* Cancer. 2013;60:1073-1082. Navari RM, et al. *N Engl J Med*. 2016;374:1356-67.
Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

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

Navari RM, et al. *N Engl J Med*. 2016;374:1356-67. Dupuis LL, et al. *Pediatr Blood Cancer*. 2016;63:1144-1151.

Standard of Care



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

Dupuis LL, et al. *Pediatr Blood Cancer.* 2011;57:191-8. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082.
Basch E, et al. *J Clin Oncol*. 2011;29:4189-98.

Serotonin Receptor Antagonists ($5HT_3RAs$)

5-HT_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

Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082. Miyajima Y et al. *Am J Pediatr Hematol Oncol.* 1994;16(3):236-41. Constenla M. *Ann Pharmacother.* 2004;38:1683-91.

Ondansetron: 1st Generation 5-HT_3RA

- First in class
- 2012 FDA label change
  - Peak concentration associated with increased risk of Torsades de Pointes
- Pediatrics: 0.25 mg/kg (max 16 mg) IV Q4H x 2 doses
- IVCI = single dose = multiple daily doses

Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082. Seynaeve C, et al. *Br J Cancer.* 1992;66:192-197. Gandara DR, et al. *Support Care Cancer.* 1998;6:237-43. Constenla M. *Ann Pharmacother.* 2004;38:1683-91.

Granisetron: 1st Generation 5-HT_3RA

- 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	Komada, 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)	• 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

Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082. Miyajima Y, et al. *Am J Pediatr Hematol Oncol.* 1994;16(3):236-41. Komada Y, et al. Eur J Cancer. 1999;35(7):1095-1101. Mabro M, et al. *Bull Cancer* 2000;87:259-64. Lexi-Comp® Pediatric and Neonatal Lexi-Drugs. Granisetron. Last update 7/29/2016 (accessed 8/10/2016).

Palonosetron: 2nd Generation 5-HT_3RA

- 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_3RAs
- 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

ALOXI® (palonosetron HCl) injection for IV use. Package Insert. 2013 Eisai Inc. Revised 09/2014 (accessed 1/5/2016).

Palonosetron in Pediatrics

- Phase III, randomized, double-blind, double-dummy, non-inferiority trial
  - 1°endpoint: Non-inferiority of PALO vs. OND for acute CINV (δ = -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)

Kovacs G, et al. *Lancet Oncol*. 2016;17:332-44.

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

Kovacs G, et al. *Lancet Oncol*. 2016;17:332-44.

Palonosetron Efficacy & Safety

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

- 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

Kovacs G, et al. *Lancet Oncol*. 2016;17:332-44.

PALO: What We Know From Adults

Highly Emetogenic Chemotherapy (HEC)		
	Acute	**Delayed**
(+) DEX	PALO = GRAN (~70%) PALO = OND (~60%)	PALO (57%) > GRAN (45%) PALO (41%) > OND (25%)
(-) DEX	PALO = GRAN (~68%)	PALO = GRAN (68%)

Moderately Emetogenic Chemotherapy (MEC)		
	Acute	**Delayed**
(+) DEX	-	-
(-) DEX	PALO (81%) > OND (69%)	PALO (74%) > OND (55%)

Gralla R, et al. *Ann Oncol*. 2003;14(10):1570-7. Tian W, et al. *Med Oncol*. 2011;28:71-8. Aapro M, et al. *Ann Oncol*. 2006;17(9):1441-49. Saito M, et al. *Lancet Oncol.* 2009;10:115-24.

Palonosetron: Summary

- Kang, et al 2015 (Pediatrics)
  - 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 $5HT_3$RAs with DEX (OR 1.14; 95% CI 0.88-1.49)
  - For delayed CINV, PALO is superior to other $5HT_3$RAs 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

Kovacs G, et al. *Lancet Oncol*. 2016;17:332-44. Popovic, et al. *Support Care Cancer*. 2014;22:1685-97.

ARS Question

- RH is a 4 year-old (18 kg, 110 cm, 0.74 m^2) 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

$5HT_3RA$ of Choice - Pediatrics

Ondansetron	Granisetron	Palonosetron
• Most experience • Highest risk of QTc prolongation? • Multiple dosing formulations • Multiple dosing schedules	• Weak literature to support pediatric dosing • Similar safety and efficacy to ondansetron	• 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

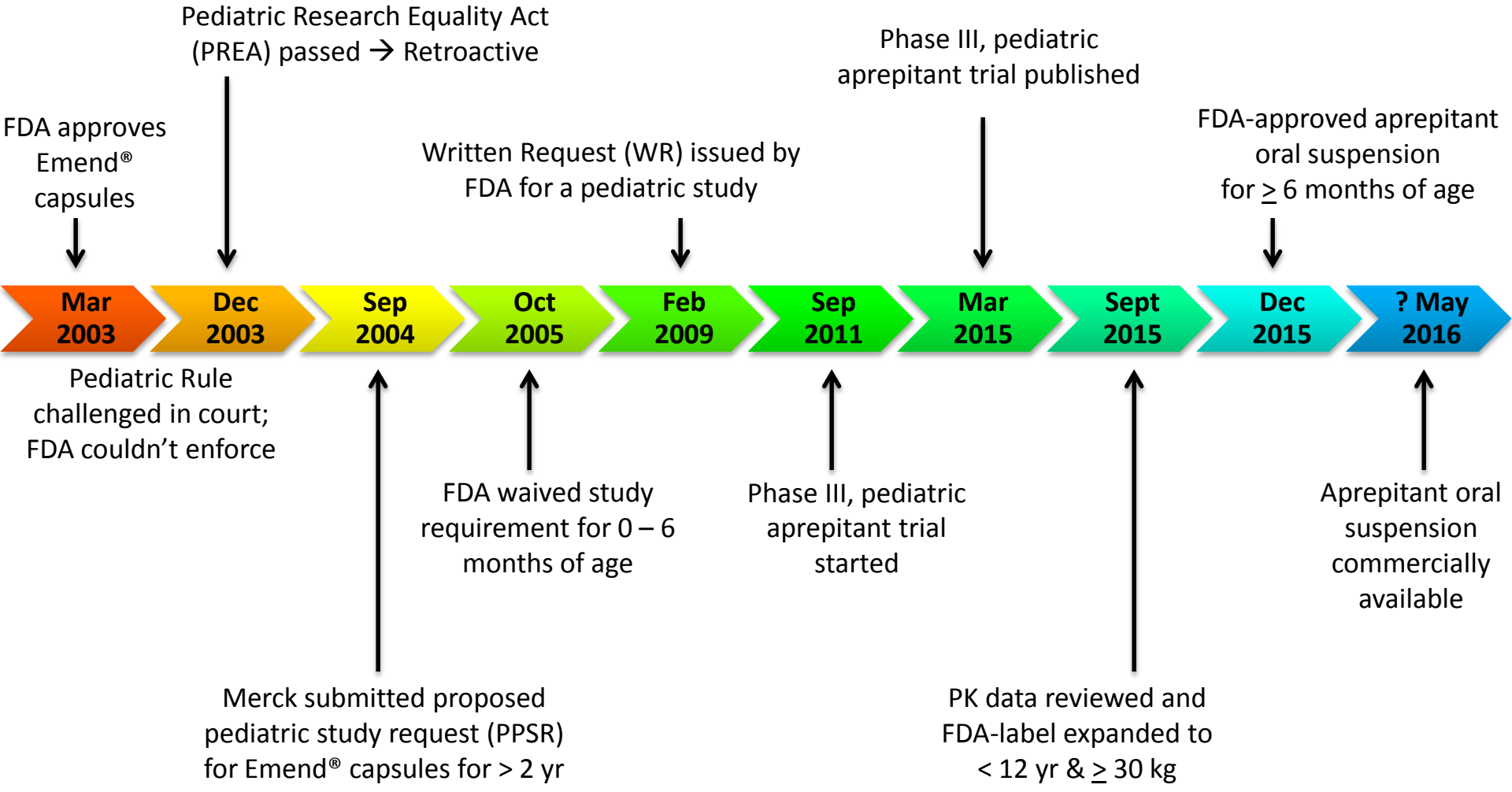
Kovacs G, et al. *Lancet Oncol*. 2016;17:332-44. Popovic, et al. *Support Care Cancer*. 2014;22:1685-97. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082

NK_1 Receptor Antagonist

NK_1 Receptor Antagonist

- Blocks substance P from activating the neurokinin-1 (NK_1) receptors in the CNS
- Augments effects of $5HT_3$RAs and dexamethasone
- Potentially significant drug-drug interactions
  - CYP3A4 substrate, inhibitor & inducer
  - CYP2C9 inducer
- Aprepitant recently studied in pediatric patients

The Aprepitant Story



Aprepitant in Pediatrics

- Phase 3, multi-center, double-blind, randomized trial
  - 1° endpoint: CR during delayed phase ($CR_{25\text{-}120h}$) 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)

Kang HJ, et al. *Lancet Oncol* 2015;16:385-94.

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)

Kang HJ, et al. *Lancet Oncol* 2015;16:385-94.

Aprepitant in Pediatrics

	APREP/OND ± DEX (n = 152)	OND ± DEX (n = 150)	P-value
Delayed ($CR_{25\text{-}120h}$) – ALL	51%	26%	< 0.0001
HEC	42%	20%	--
No HEC	66%	39%	--
Acute ($CR_{0\text{-}24h}$) – ALL	66%	52%	0.0135
HEC	65%	51%	--
No HEC	70%	55%	--
Overall ($CR_{0\text{-}120h}$) – ALL	40%	20%	0.0002
HEC	35%	14%	--
No HEC	49%	33%	--

"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

Kang HJ, et al. *Lancet Oncol.* 2015;16:385-94.

ARS Question

- BT is a 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

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 (not available): 25 mg/mL with 72-hr stability
  - Published extemporaneous compound 20 mg/mL with 90-day stability

Kang HJ, et al. *Lancet Oncol.* 2015;16:385-94. Lexi-Comp® Pediatric and Neonatal Lexi-Drugs. Aprepitant. Last updated 8/2/2016 (accessed 8/10/2016).

Future Standard of Care for Prevention of Pediatric CINV

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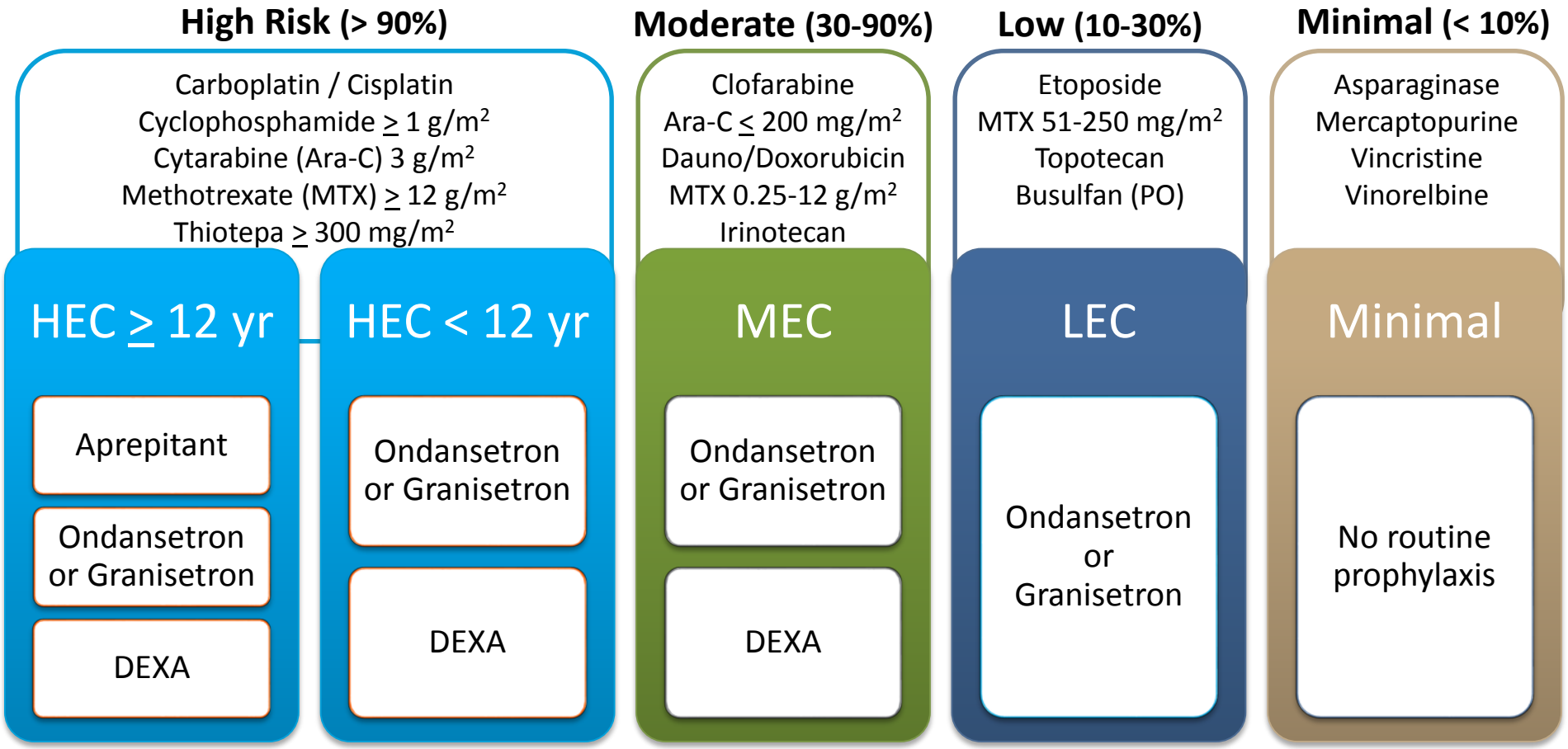
2016: Prevention of Acute CINV

- To be published in Sept – hopefully update with graphic prior to presentation, if not, will remove slide and tell audience to look for the publication in the near future and will summarize the key points in the presentation summary

Standard of Care



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

Dupuis LL, et al. *Pediatr Blood Cancer.* 2011;57:191-8. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082.
Basch E, et al. *J Clin Oncol*. 2011;29:4189-98.

Treatment of Breakthrough CINV

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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

Dupuis LL, et al. *Pediatr Blood Cancer.* 2011;57:191-8. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082.
Basch E, et al. *J Clin Oncol*. 2011;29:4189-98.

Breakthrough CINV

Common Agents

- Diphenhydramine
- Dronabinol
- Hydroxyzine
- Lorazepam
- Metoclopramide
- Prochlorperazine
- Scopolamine

Newer or Controversial Agents

- Aprepitant
- Dexamethasone
- Fosaprepitant
- Haloperidol
- Olanzapine
- Palonosetron

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!

Dupuis LL, et al. *Pediatr Blood Cancer.* 2011;57:191-8. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082.
Basch E, et al. *J Clin Oncol*. 2011;29:4189-98.

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

ARS Question

- 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

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
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Diphenhydramine
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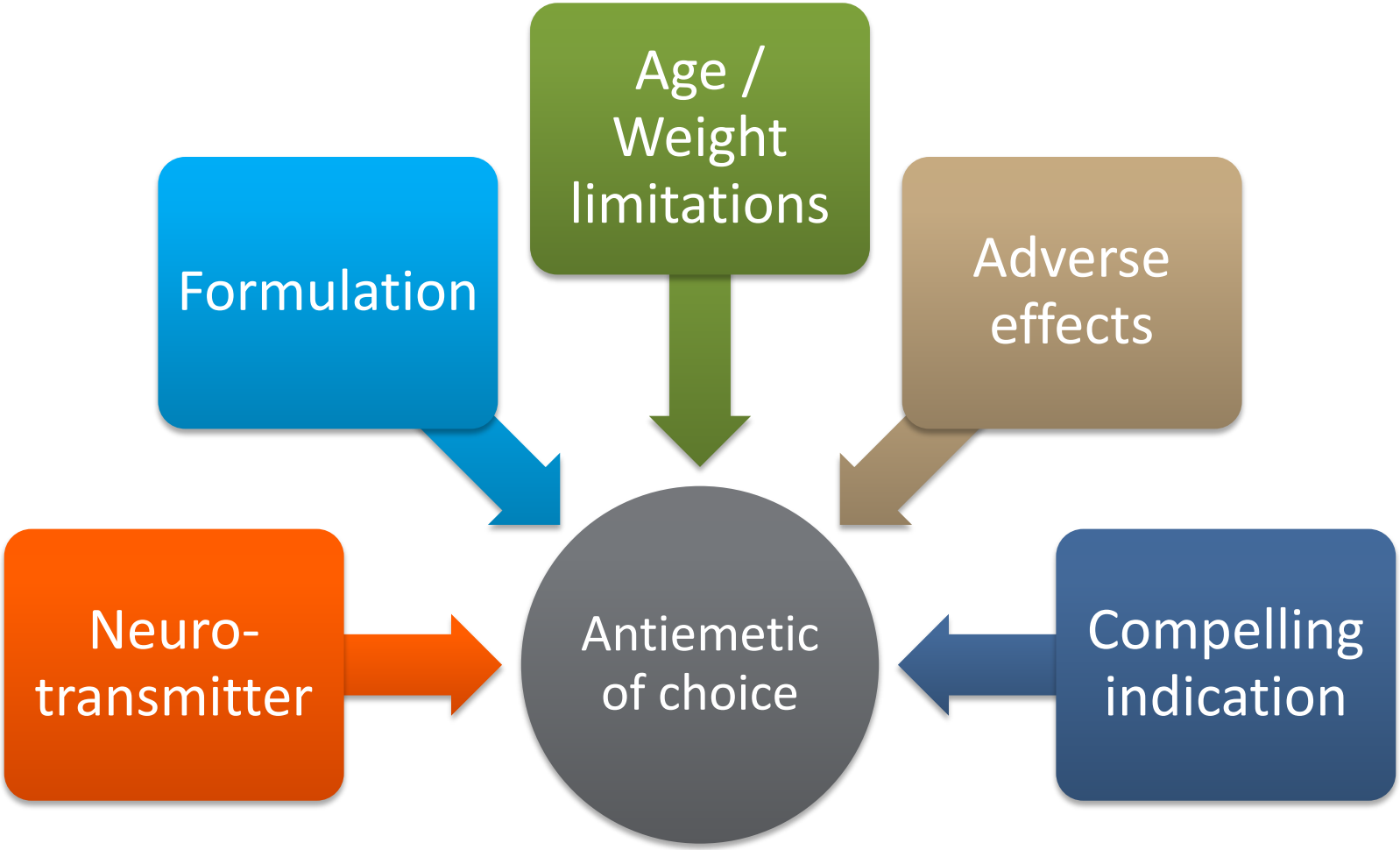
Olanzapine
Promethazine
Scopolamine patch

Ondansetron IVCI
Granisetron
Palonosetron

Dupuis LL, et al. *Pediatr Blood Cancer.* 2011;57:191-8. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082.
Basch E, et al. *J Clin Oncol*. 2011;29:4189-98.

Decisions, Decisions



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-HT_{2A}, 5-HT_{2C}, D_{1-4}, H_1 and α_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

Navari RM, et al. *Support Care Cancer*. 2013;21:1655-63. Navari RM, et al. *J Support Oncol.* 2011;9(5):188-95.

Olanzapine for CINV (Adults)

- NCCN Guidelines Version 2.2016
  - HEC/MEC Acute and Delayed Prevention option
    - —NK_1RA + $5HT_3RA$ + DEX
    - —OLZ 10 mg PO daily + PALO + DEX
  - Breakthrough CINV options
    - —Add OLZ 10 mg PO daily (over metoclopramide)
    - —Consider changing from NK_1-containing regimens to OLZ-containing regimen, or vice versa

Antiemesis. NCCN Guidelines®. National Comprehensive Cancer Network. Version 2.2016 (accessed 8/10/2016).

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

Flank J, et al. *Pediatr Blood Cancer*. 2015;62:496-501.

Pros of Breakthrough CINV Agents

Agent	Compelling Indication									
	Acid reflux	Anxiety	Appetite	Constipation	Depressed Mood	Diarrhea	Headache	Insomnia	Travel Sickness	Notes
Diphenhydramine								Yes	Yes	Over the counter
Dronabinol			Yes		Yes					
Famotidine	Yes									Over the counter
Haloperidol		Yes						Yes		
Hydroxyzine								Yes	Yes	
Lorazepam		Yes						Yes		
Metoclopramide				Yes		No	Yes			
Olanzapine		Yes	Yes		Yes			Yes		Oral disintegrating tablet
Palonosetron				No		Yes				Long acting
Promethazine								Yes	Yes	
Scopolamine				No		Yes			Yes	Transdermal patch Q72H

Freedman JL, et al. *Pediatr Blood Cancer.* 2014;61:1798-1805. Kang HJ, et al. *Lancet Oncol.* 2015;16:385-94. Rodgers C, et al. *Cancer Nursing.* 2012;35(3):203-10. Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

Cons of Breakthrough CINV Agents

Agent	Contraindications/Precautions									
	Oral	IV	↓ CNS	↓ WBC	Age/Wt limit	QTc prolonging	EPS risk	Paradoxical effect	Anti-cholinergic	Notes
Aprepitant	Yes	No			≥ 12 yr or ≥ 30 kg					Insurance coverage; Drug interactions (CYP3A4)
Diphenhydramine	Yes	Yes						Yes	Yes	
Dronabinol	Yes	No	Yes							May ↓ seizure threshold; May worsen psych disorders; Contains sesame oil
Famotidine	Yes	Yes		Yes		Yes				GERD
Haloperidol	Yes	Yes	Yes	Yes	≥ 3 yr	Yes	Yes			
Hydroxyzine	Yes	No						Yes	Yes	
Lorazepam	Yes	Yes	Yes					Yes		Anxiolytic; Risk of dependence
Metoclopramide	Yes	Yes					Yes			↑ GI motility
Olanzapine	Yes	No	Yes	Yes			Yes			Drug interactions ($5HT_3$); ↑LFTs
Palonosetron	No	Yes			≥ 1 mon					Constipation; Headache
Promethazine	Yes	Yes		Yes	≥ 2 yr	Yes		Yes		< 2 yr respiratory depression (BBW)
Scopolamine	No	No			≥ 13 yr				Yes	Patch contains aluminum (MRI)

Freedman JL, et al. *Pediatr Blood Cancer.* 2014;61:1798-1805. Hesketh PJ. *N Engl J Med.* 2008;358:2482-94.

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

Diphenhydramine
Dronabinol
Haloperidol
Hydroxyzine
Lorazepam
Metoclopramide
Olanzapine
Promethazine
Scopolamine patch

3. Switch

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

Ondansetron IVCI
Granisetron
Palonosetron

Dupuis LL, et al. *Pediatr Blood Cancer.* 2011;57:191-8. Dupuis LL, et al. *Pediatr Blood Cancer*. 2013:60:1073-1082.
Basch E, et al. *J Clin Oncol*. 2011;29:4189-98.

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

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

- The 5-HT_3RAs are the cornerstone to preventing CINV, however the optimal 5-HT_3RA 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

Management of Pediatric Chemotherapy-Induced Nausea and Vomiting: A Complex Case

Jennifer Thackray, PharmD, BCPS, BCPPS

Pediatric Oncology Clinical Pharmacy Specialist

Memorial Sloan Kettering Cancer Center

New York, New York

accp American College of Clinical Pharmacy

ashp Certification Resources