DATE ON MANAGEMENT OF NAUSEA AND VOMITING FOR CANCER PATIENTS

Kai Zheng, PharmD, MS
PGY1 Pharmacy resident
Avera McKennan Hospital & University Health Center

Disclosure statement

- ***I have had no financial relationship over the past 12 months with any commercial sponsor with a vested interest in this presentation.***

Objective for pharmacists

- Learning gaps: New NCCN and ASCO guideline for nausea and vomiting management updated in 2017
- Explain the risk factor of nausea and vomiting
- Evaluate key medications utilized in treating nausea and vomiting for cancer patients in a comprehensive treatment regimen
- Describe potential complications that may develop from treating nausea and vomiting for cancer patients in a comprehensive treatment regimen

Koth et.al, Am J Health-Syst Pharm. 2017;74:812-19

Objective for technicians

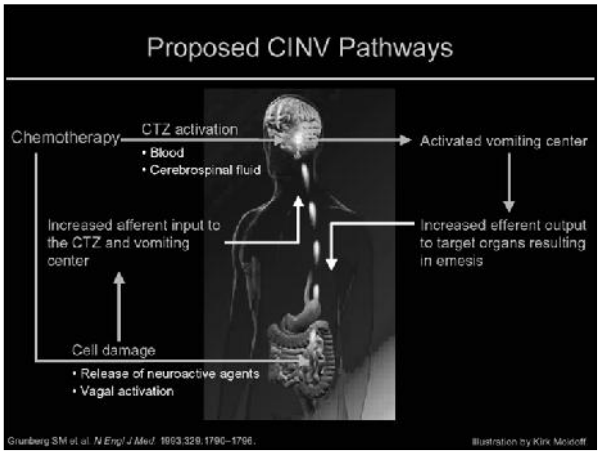
- Learning gaps: New NCCN and ASCO guideline for nausea and vomiting management updated in 2017
- Describe the epidemiology of nausea and vomiting caused by chemotherapy
- Evaluate key medications utilized in treating nausea and vomiting for cancer patients in a comprehensive treatment regimen

Chemotherapy-Induced Nausea and Vomiting (CINV): why it is important?

- Up to 80% of patients receiving chemotherapy report some degree of nausea or vomiting
- Impact patient's physical and mental status
- Degenerate self-care and ability to do activities of daily life
- Withdrawal from potentially useful or curative antineoplastic therapy
- Metabolic disorders / Electrolyte disorders
- Nutritional depletion, anorexia

Chemotherapy induced nausea and vomiting (CINA) -- 3 categories

- **Acute emesis**: usually begins within 1-2 hours of chemotherapy and peaks in 4-6 hours
- **Delayed emesis**: begins more than 24 hours after chemotherapy
- **Anticipatory emesis**: occurring prior to treatment as a conditioned response in patients who had significant (poor controlled) N/V from previous chemotherapy



Patient Risk Factors for CINV

- Age: <50 yo
- Gender: Females > Males
- History of Nausea / Vomiting:
  - Increased with History of motion sickness, morning sickness with pregnancy
- History of Alcohol Use Heavy use = lower risk of nausea, vomiting
  - Decreased in individuals with > 10 drinks/week

Principles of emesis control for cancer patients

- Prevention of N/V is the goal
- There are other potential causes of emesis in cancer patient than chemotherapy
  - bowel obstruction, brain metastases, electrolyte imbalance, radiation therapy
- Choice of antiemetic:
  - Based upon emetic risk, prior experience and patient factors
- For multi-drug regimens, select antiemetic therapy based on the drug with highest emetic risk

Chemotherapy Agent Classification

- FOUR EMETIC RISK GROUPS

HIGH (HEC)	Risk in nearly all patients (>90%)
MODERATE (MEC)	Risk in 30 to 90% of patients
LOW (LEC)	Risk in 10 to 30% of patients
MINIMAL	Fewer than 10% at risk

Common antiemetic agents

- **5-Hydroxytrptamine (5-HT3) receptor antagonists**
  - First generation: ondansetron, dolasetron, granisetron
  - Second generation: palonosetron (t1/2 40hr)
- **Neurokinin-1 (NK-1) receptor antagonists**
  - Aprepitant (oral), fosaprepitant (IV)
  - Rolapitant
  - Netupitant and palonosetron (Akynzeo)
- **Steroid**
  - Dexamethasone
- **Olanzapine (new)**

Guidelines key updated in 2017: ASCO

Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline: October 2017

- Add olanzapine: patients receiving high emetic risk chemotherapy or suffering break through nausea and vomiting
- Limit dexamethasone to day 1 only: patients receiving anthracycline and cyclophosphamide chemotherapy
- Add NK-1 antagonist: patients receiving carboplatin AUC ≥4 mg/ml per minute

Hesketh P, et al. J Clin Oncol. 2017 Oct 1; 35(28):3240-3261

Guidelines key updated in 2017: NCCN

NCCN-antiemetic guideline Version 2.2017: March 2017

- High emetic risk IV chemotherapy: new option
  - Four antiemetic agents including: olanzapine, 5-HT3 receptor antagonist, NK1 receptor antagonist and dexamethasone
- Granasetron extended-release formulation is specifically for SubQ administration and is not interchangeable with the IV formulation.
  - The extended-formulation should not be administered at less than one week intervals.

NCCN guideline: Antiemeitcs, Version 2.2017, March 28,2017.

Guidelines comparison- High emetic risk agents

	ASCO 2017	NCCN 2017
Cisplatin and other High emic risk agents	• NK-1 receptor antagonist, 5-HT3 receptor antagonist, dexamethasone, and olanzapine on day 1. • Dexamethasone and olanzapine should be continued on days 2-4.	
Anthracycline combined with cyclophosphamide day1	NK-1 receptor antagonist, 5-HT3 receptor antagonist, dexamethasone, and olanzapine.	
Anthracycline combined with cyclophosphamide day2-4	Continue olanzapine on day 2-4.	Continue olanzapine AND dexamethasone on day 2-4 (same as above)
All high emetic risk agents	No three agents option	Other three agents options without olanzapine

NCCN guideline: Antiemeitcs, Version 2.2017, March 28,2017.
Hesketh P, et al. J Clin Oncol. 2017 Oct 1; 35(28):3240-3261

Guidelines comparison-Moderate emetic risk agents

ASCO 2017	NCCN 2017
Carboplatin AUC≥ 4: NK1 antagonist, 5-HT3 antagonist and dexamethasone	5-HT3 antagonist, dexamethasone, NK1 antagonist
Excluding carboplatin AUC≥4: 5-HT3 antagonist and dexamethasone	5-HT3 antagonist (prefer palonosetron or extended-release granisetron injection) and dexamethasone
	Palonosetron, olanzapine and dexamethasone

NCCN guideline: Antiemeitcs, Version 2.2017, March 28,2017.
Hesketh P, et al. J Clin Oncol. 2017 Oct 1; 35(28):3240-3261

Guidelines comparison- Multiday Chemotherapy

ASCO 2017	NCCN 2017
Patients treated with multiday chemotherapy should receive antiemetics before administration of chemotherapy on each day and for 2 days after the completion of the antineoplastic regimen.	Designing the antiemetic regimen should consider administration setting (inpatient or outpatient), route (IV, oral or transdermal), adherence/compliance issues, and individual risk factors.
Patient treated with 4- or 5-day cisplatin regimen should be offered a three-drug combination of an NK1antagonist, a 5-HT3 antagonist, and dexamethasone	**Dexamethasone:** once daily on chemo days, then continued for 2-3 days after regimens likely to cause delayed emesis. **5-HT3:** prefer palonosetron or granisetron extended-release injection if not including NK1 antagonist **NK1 antagonist**: For oral aprepitant, limited data support administer aprepitant on days 4 and 5

NCCN guideline: Antiemeitcs, Version 2.2017, March 28,2017.
Hesketh P, et al. J Clin Oncol. 2017 Oct 1; 35(28):3240-3261

Guidelines comparison- Breakthrough nausea and vomiting

ASCO 2017	NCCN 2017

• Add olanzapine if patient not already receive this medication.
• Add a drug from a different class if patient already receive olanzapine.
  • NK-1 antagonist
  • Lorazepam or alprazolam
  • Metoclopramide
  • Dronabinol or nabilone
	• Prevention is much more effective than treatment
	• Add an agent from a different class
	• Oral route is not likely to be feasible
	• For next cycle:
	  • Add NK-1 antagonist if not already included
	  • NK-1 antagonist to replace olanzapine or vice versa
	  • Combine NK-1 antagonist and olanzapine
	  • Consider adding an anxiolytic agent

NCCN guideline: Antiemeitcs, Version 2.2017, March 28,2017.
Hesketh P, et al. J Clin Oncol. 2017 Oct 1; 35(28):3240-3261

Guidelines comparison-Anticipatory emesis

ASCO 2017	NCCN 2017
All patients should receive the most active antiemetic regimen that is appropriate for the antineoplastic agents being administered.	Prevention is Key: use optimal antiemetic therapy and avoid strong smells that may precipitate symptoms
Behavioral therapy may help patients already experienced anticipatory emesis.	Behavioral therapy
	Alprazolam 0.5-1 mg or lorazepam 0.5-2 mg po beginning on the night before chemotherapy and then repeated the next day 1-2 hrs before chemohterapy

NCCN guideline: Antiemeitcs, Version 2.2017, March 28,2017.
Hesketh P, et al. J Clin Oncol. 2017 Oct 1; 35(28):3240-3261

Olanzapine

- Randomized, Double-blind, Phase 3 trail (n=380, per protocol)
- Chemotherapy naïve patients receiving either cisplatin ($\geq$70mg/m^2) or cyclophosphamide-doxorubicin (600-60mg/m^2).
- Patients were receiving 5HT3 antagonist, NK-1 antagonist and dexamethasone PLUS either olanzapine 10mg daily po or placebo on day 1-4.
- Assessment period: 0-120 hrs
- Primary outcome: nausea prevention, measured by visual analog scale.
- Secondary outcome: no emesis and no use of rescue medication (complete response), based on patient's daily record.

Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. N Engl J Med. 2016 Jul 14;375(2):134-42.

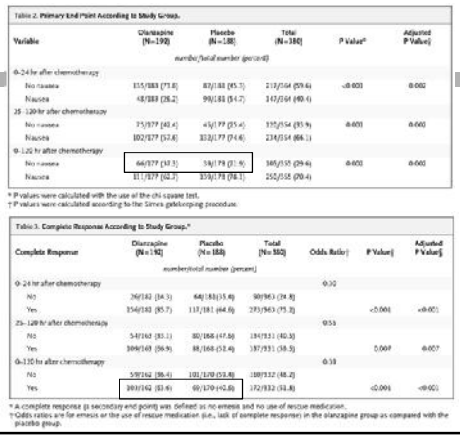


Table 2. Primary End Point According to Study Group.

Variable	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	P Value*	Adjusted P Value†
	number/total number (percent)				
0–24 hr after chemotherapy					
No nausea	155/183 (77.0)	87/183 (45.7)	213/364 (59.6)	<0.001	0.002
Nausea	48/183 (26.2)	99/181 (54.7)	147/364 (40.4)		
25–120 hr after chemotherapy					
No nausea	75/177 (42.4)	45/177 (25.4)	120/354 (33.9)	0.001	0.002
Nausea	102/177 (57.6)	132/177 (74.6)	234/354 (66.1)		
0–120 hr after chemotherapy					
No nausea	66/177 (37.3)	39/179 (21.8)	105/135 (29.6)	0.001	0.002
Nausea	111/177 (62.7)	140/179 (78.2)	252/356 (70.4)		

* P values were calculated with the use of the chi-square test.
† P values were calculated according to the Simes gatekeeping procedure.

Table 3. Complete Response According to Study Group.*

Complete Response	Olanzapine (N=192)	Placebo (N=188)	Total (N=380)	Odds Ratio†	P Value‖	Adjusted P Value‖
	number/total number (percent)					
0–24 hr after chemotherapy				0.30		
No	26/182 (14.3)	64/181 (35.4)	90/363 (24.8)			
Yes	156/182 (85.7)	117/181 (64.6)	273/363 (75.2)		<0.001	<0.001
25–120 hr after chemotherapy				0.53		
No	54/162 (33.3)	80/168 (47.6)	134/331 (40.5)			
Yes	108/162 (66.7)	88/168 (52.4)	197/331 (59.5)		0.007	0.007
0–120 hr after chemotherapy				0.38		
No	59/162 (36.4)	101/170 (59.4)	160/332 (48.2)			
Yes	103/162 (63.6)	69/170 (40.6)	172/332 (51.8)		<0.001	<0.001

* A complete response (a secondary end point) was defined as no emesis and no use of rescue medication.
† Odds ratios are for emesis or the use of rescue medication (i.e., lack of complete response) in the olanzapine group as compared with the placebo group.

Olanzapine

- Averse events
  - Sedation
  - Drowsiness
  - Increase in appetite
- Drug-drug interactions
  - Other antipsychotic
  - Metoclopramide or other dopamine receptor antagonists.

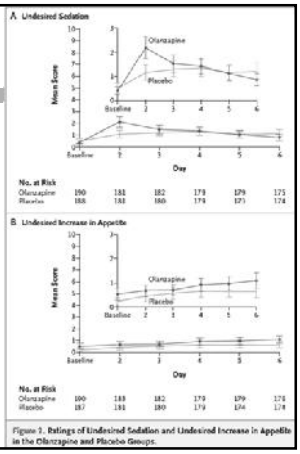


Figure 2. Ratings of Undesired Sedation and Undesired Increase in Appetite in the Olanzapine and Placebo Groups.

Rolapitant

- FDA approved in September 2015
- MOA: Substance P/NK1receptor antagonist
- Half-life elimination: ~7 days
- Do not administer rolapitant at less than 2-week intervals
- Does NOT induce or inhibit the CYP3A4 pathway
- No need to adjust concomitant dexamethasone dose
- Inhibits CYP2D6 pathway
- FDA Safety Alert January 2018: anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions to rolapitant injection

Varubi (rolapitant) [prescribing information]. Waltham, MA: Tesaro Inc; October 2017.

Rolapitant

- Two randomized, double-blind, active-controlled, phase 3 trials: HEC-1 and HEC-2
- Patients receiving cisplatin therapy (≥60 mg/m^2) for first time
- Patients receiving either rolapitant 180mg po (n=264, 271) or matching placebo (n=262, 273) 1-2hr before cisplatin chemotherapy.
- All patients receive granisetron plus dexamethasone about 30mins before chemotherapy, and dexamethasone on days 2-4.
- Primary outcome: proportion of patients with no emesis or use of rescue medication in the delayed phase >24-120hr after chemotherapy.
- Secondary outcome: proportion of patients with no emesis or use of rescue medication in acute (0-24hr) and overall phase (0-120hr).

Rapoport BL et al. Lancet Oncol. (2015)

Rolapitant

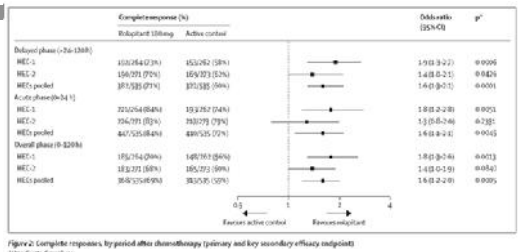


Figure 2: Complete responses, by period after chemotherapy (primary and key secondary efficacy endpoint)
*Unadjusted p-values.

- Safety: Well tolerated, no significant different from control group
- Most common ADR: headache, constipation, dyspepsia and hiccups

Rapoport BL et al. Lancet Oncol. (2015)

Granisetron extended-release injection

- FDA approved in August 2016
- MOA: 5-HT3 antagonist
- Extended-release, SubQ injection with a half life ~24 hrs
- Do not administer granisetron SubQ injection at less than 1-week intervals
- Granisetron is also available in IV solution, oral tablet, and subcutaneous patch

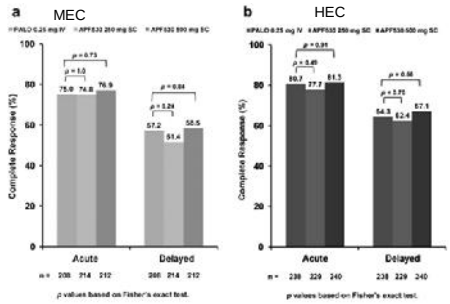
Sustol (granisetron) extended-release injection [prescribing information]. Redwood City, CA: Heron Therapeutics; November 2017.

Granisetron extended-release injection

- Randomized, double-blind, parallel-group phase 3 trail
- Patients receiving single-day moderately or highly emetogenic chemotherapy (MEC or HEC)
- Patients receiving granisetron 5mg (APF530 250mg) SubQ plus placebo IV, granisetron 10mg (APF530 500mg) SubQ plus placebo IV or plalonosetron IV plus placebo SubQ
- Primary objective 1: establish granisetron extended-release SubQ non-inferior to palonosetron IV in preventing acute CINV (0-24hr) following MEC or HEC
- Primary objective 2: establish granisetron extended-release SubQ non-inferior to palonosetron IV in preventing delayed CINV (24-120hr) following MEC
- Primary objective 3: establish granisetron extended-release SubQ superior to palonosetron IV in preventing delayed CINV (24-120hr) following HEC

Raftopoulos H, Support Care Cancer. 2015 Mar;23(3):723-29.

Granisetron extended-release injection



Raftopoulos H, Support Care Cancer. 2015 Mar;23(3):723-29.

Granisetron extended-release injection

- Conclusion
  - Acute CINV: Non-inferior to palonosetron after MEC and after HEC
  - Delayed CINV: Non-inferior to palonosetron after MEC but not superior to palonosetron after HEC either

Raftopoulos H, Support Care Cancer. 2015 Mar;23(3):723-

Patient case

- 45-year-old woman recently diagnosed with breast cancer. Her diagnosis has caused her some anxiety and depression. She is a social drinker, less than 10 drinks per year. Her PMH is significant for morning sickness and motion sickness. Her oncologist wishes to treat her with cyclophosphamide 600 mg/m^2 and doxorubicin 60 mg/m^2 every 14 days.
- What risk factors for CINV she has?
- What antiemetic treatment should she receive?

Patient case continued

Risk factors for CINV:

- Age< 50yo
- Female
- History of morning sickness and motion sickness
- Not a heavy alcohol drinker

Patient case continued

- Patient will receive:
  - Palonosetron 0.25mg on day 1
  - Fosaprepitant 150mg IV on day 1
  - Dexamethasone 12mg on day 1, (then 8mg daily on day 2 through 4)
  - Olanzapine 10mg day 1-4
- What else may be considered?

Take home messages

- ASCO and NCCN recommend similar regimen to prevent and treat chemotherapy induced nausea and vomiting
- Rolapitant is a new NK-1 antagonist combined with 5-HT3 and dexamethasone that is work for entire 120hrs after cisplatin based chemotherapy
- Granisetron extended-release injection has comparable anti-emetic effect over entire 120hrs after MEC and HEC.
- Olanzapine is now being incorporated into the strategy for prevention of and breakthrough nausea and vomiting in highly emetic chemotherapy regimens

References

- Hesketh PJ, Kris MG, Basch E, et al. Antiemetics: American Society of Clinical Oncology Clinical Practice Guideline Update, J Clin Oncol. 2017 Oct 1; 35(28):3240-3261
- NCCN guideline: Antiemeitcs, Version 2.2017, March 28, 2017.
- Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting. N Engl J Med. 2016 Jul 14;375(2):134-42.
- Hesketh PJ, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109
- Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity-state of the art. Support Care Cancer. 2010;19:S43-47.
- Rapoport BL, Chasen MR, Gridelli C, et al. Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of cisplatin-based highly emetogenic chemotherapy in patients with cancer: two randomised, active-controlled, double-blind, phase 3 trials. Lancet Oncol. 2015;16(9):1079-1089
- Raftopoulos H, Cooper W, O'Boyle E, et al. Comparison of an extended-release formulation of granisetron (APF530) versus palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately or highly emetogenic chemotherapy: results of a prospective, randomized, double-blind, noninferiority phase 3 trial. Support Care Cancer. 2015 Mar;23(3):723-32.