Chemotherapy Induced Nausea and Vomiting

Hong Yu Wen
Senior Clinical Pharmacist, SGH

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Learning Objectives

1. List patient-specific risk factors for developing nausea (N) or vomiting (V)
2. Define acute, breakthrough, delayed, and anticipatory N/V
3. Design an appropriate antiemetic regimens and treatment strategies for:
    a) Acute N/V
    b) Delayed N/V
    c) Breakthrough N/V
    d) Anticipatory N/V

Case 1 (Mrs XYZ)

- 31 y/o Chinese lady
- Married, has 1 child
- Social History
  - No alcohol, tobacco use
- Medical history
  - Motion sickness (gets nauseated on boats)
  - Hyperemesis with pregnancy
  - Asthma

Case 1 (Mrs XYZ)

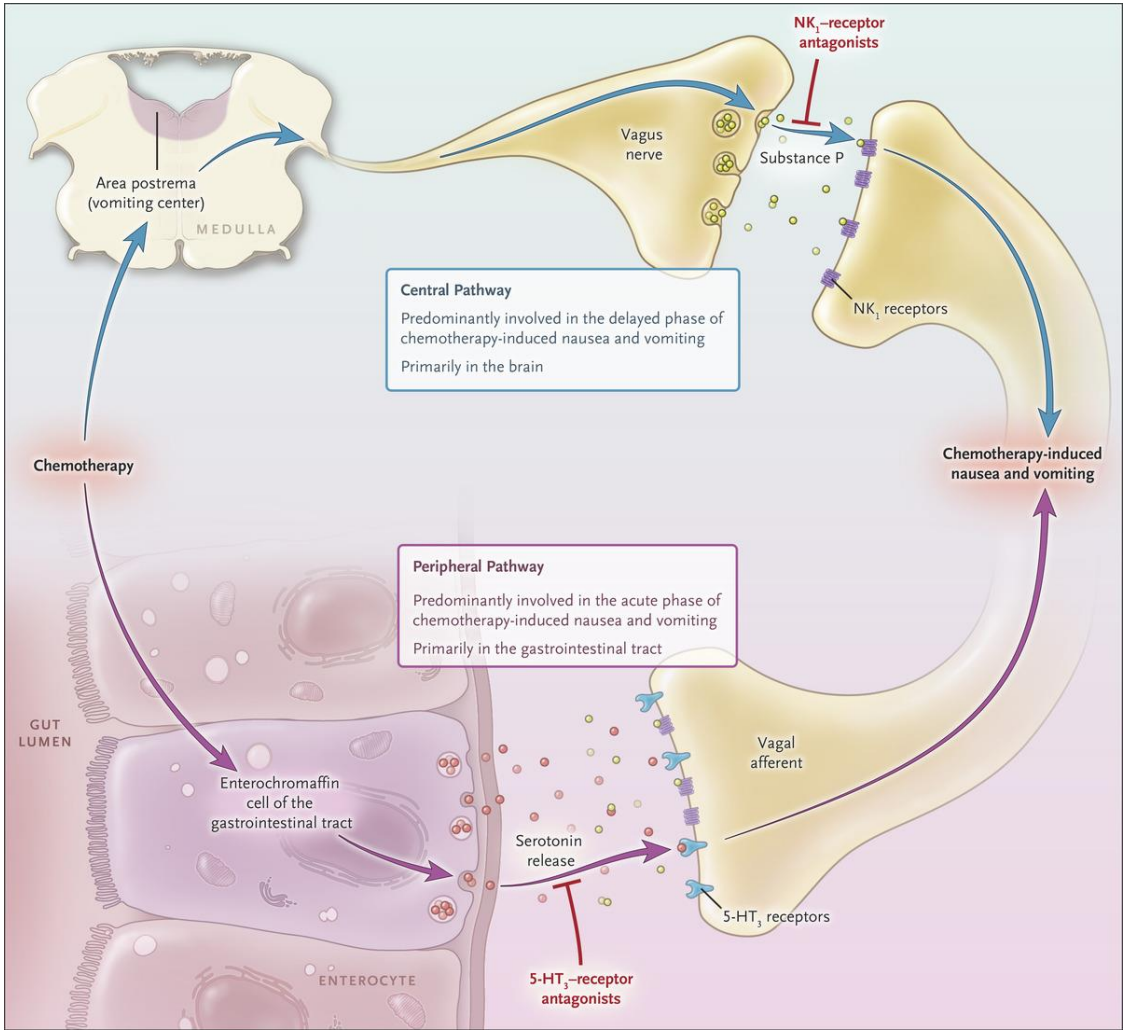
- Presenting complain:
  - Found a lump through her monthly Breast Self Examination
- Diagnosis: Stage II Breast Ca (ER/PR –ve, HER2 -ve)
- Due to receive first cycle of adjuvant chemotherapy (AC) after lumpectomy

Drug	Dose	Days
Doxorubicin	60mg/m^2	D1
Cyclophosphamide	600mg/m^2	D1

Case 1

- What are the risk factors for CINV in Mrs XYZ's case?
- What would be an appropriate antiemetic regimen for her?
- Any non-pharmacological counselling points?
- XYZ was very nervous about her first chemotherapy treatment. Before she came to the clinic, she was experiencing nausea at home. Knowing that piece of information, what should be done with her antiemetics?

Emesis pathway



Navari RM, et al. N Engl J Med 2016; 374:1356-1367

Emesis pathway

Neurotransmitters Involved

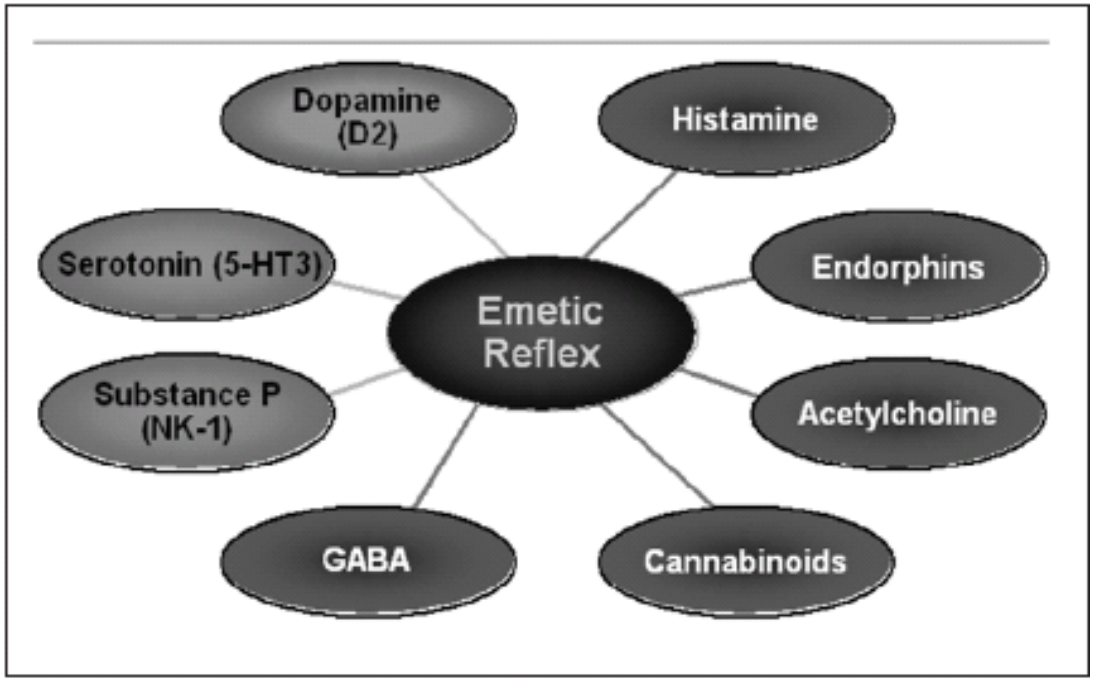
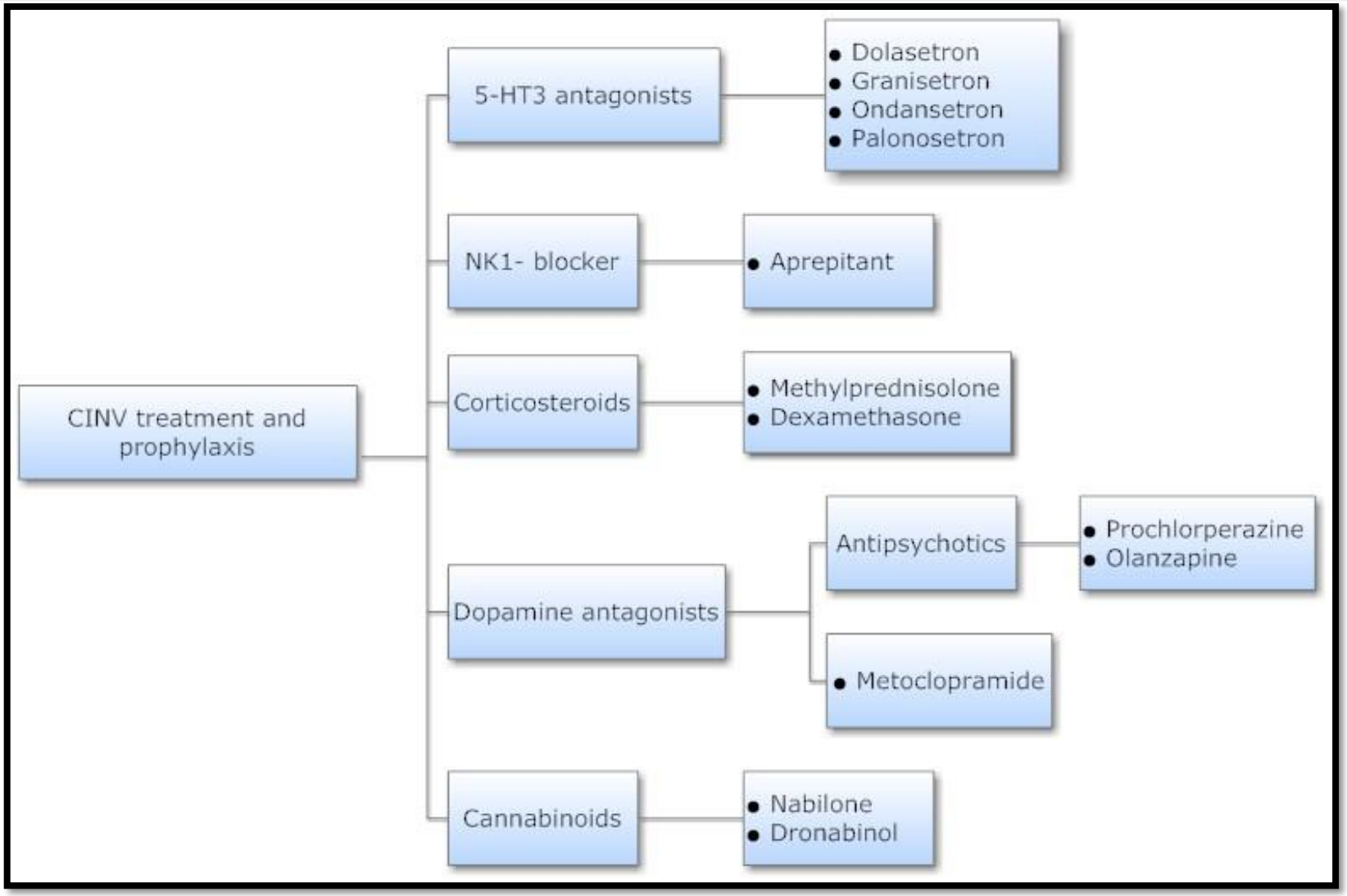


Figure 2: Neurotransmitters That May Play a Role in the Emetic Reflex—Among these, the roles of dopamine, serotonin, and substance P have been translated into clinically useful therapeutic applications. GABA = gamma-aminobutyric acid.

Hesketh PJ. Oncology (Williston Park). 2004 Sep;18(10 Suppl 6):9-14.

Antiemetic classes



Classification

Type of emesis	Details
Acute	- Occurs within mins to hrs after initiation of chemo - Usually resolves after 24hrs
Delayed	- Starts >24hrs after chemo is given - May last up to 5 to 7 days Eg. Cisplatin, Carboplatin, Cyclophosphamide, Doxorubicin
Anticipatory	- Conditioned response - Occurs before chemotherapy
Breakthrough	- Occurs despite prophylaxis
Refractory	- Nausea & vomiting not responding to treatment given

Risk factors

Table 2: Patient-related Risk Factors for Emesis Following Chemotherapy

Major Factors	Minor Factors
Female	History of Motion Sickness
Age <50 years	Emesis during past pregnancy
History of low prior chronic alcohol intake (<1 ounce of alcohol/day)	
History of previous chemotherapy-induced emesis	

Navari RM. European Oncology & Haematology, 2013;9(1):51–5.

Emetic Risk Groups

Emetic risk of Single Intravenous Antineoplastic Agents in Adults

Minimal (< 10%)

- Bevacizumab
- Bleomycin
- Busulfan
- 2-Chlorodeoxyadenosine
- Cladribine
- Daratumumab
- Fludarabine
- Nivolumab
- Obinutuzumab
- Ofatumumab
- Pembrolizumab
- Pixantrone
- Pralatrexate
- Ramucirumab
- Rituximab
- Trastuzumab
- Vinblastine
- Vincristine
- Vinorelbine

Low (10%-30%)

- Aflibercept
- Atezolizumab
- Belinostat
- Blinatumomab
- Bortezomib
- Brentuximab
- Cabazitaxel
- Carfilzomib
- Catumaxumab
- Cetuximab
- Cytarabine ≤ 1,000 mg/m²
- Docetaxel
- Elotuzumab
- Eribulin
- Etoposide
- Fluorouracil
- Gemcitabine
- Ipilimumab
- Ixabepilone
- Methotrexate
- Mitomycin

Moderate (30%-90%)

- Alemtuzumab
- Azacitidine
- Bendamustine
- Carboplatin
- Clofarabine
- Cyclophosphamide < 1,500 mg/m²
- Cytarabine > 1,000 mg/m²
- Daunorubicin
- Doxorubicin
- Epirubicin
- Idarubicin
- Ifosfamide
- Irinotecan
- Irinotecan liposomal injection
- Oxaliplatin
- Romidepsin
- Temozolomide*
- Thiotepa†
- Trabectedin

High (> 90%)

- Anthracycline/cyclophosphamide combination
- Carmustine
- Cisplatin
- Cyclophosphamide ≥ 1,500 mg/m²
- Dacarbazine
- Mechlorethamine
- Streptozocin

ASCO Antiemetic Guidelines 2017

Emetic Risk Groups – Single Oral Agents

HIGH	Hexamethylmelamine Procarbazine	
MODERATE	Cyclophosphamide Temozolomide	Vinorelbine Imatinib
LOW	Capecitabine Tegafur Uracil Etoposide Sunitinib Fludarabine	Everolimus Lapatinib Lenalidomide Thalidomide
MINIMAL	Chlorambucil Hydroxyurea Melphalan Methotrexate	6-Thioguanine Gefitinib Sorafenib Erlotinib L-Phenylalanine mustard

MASCC/ESMO Antiemetic Guidelines 2013

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Drug	Dose	Days
Doxorubicin	60mg/m^2	D1
Cyclophosphamide	600mg/m^2	D1

High Emetic Risk

NCCN 2018	ASCO 2017	MASCC/ESMO 2016
NK1 5HT3 DEX + Cont D2-4 +/- OLA + Cont D2-4	NK1 5HT3 DEX + Cont D2-4* OLA + Cont D2-4 *For AC regimens, guidelines recommend DEX only on D1 of treatment	NK1 5HT3 DEX + Cont D2-4
PALO DEX OLA + Cont D2-4		PALO DEX OLA + Cont D2-4

Olanzapine

- Randomized, double-blind, phase III trial (olanzapine vs placebo) in 380 patients receiving HEC
- Patients also received dexamethasone, aprepitant or fosaprepitant, and a 5HT3 antagonist

	Olanzapine, % (N=192)	Placebo, % (N=188)	P value
No Nausea			
At 24h	74	45	0.002
25 to 120h	42	25	0.002
Overall	37	22	0.002
CR Rate			
At 24h	86	65	<0.001
25 to 120h	67	52	0.007
Overall	64	41	<0.001

Navari RM, et al. N Engl J Med. 2016;375(2):134-142.

Recent Developments

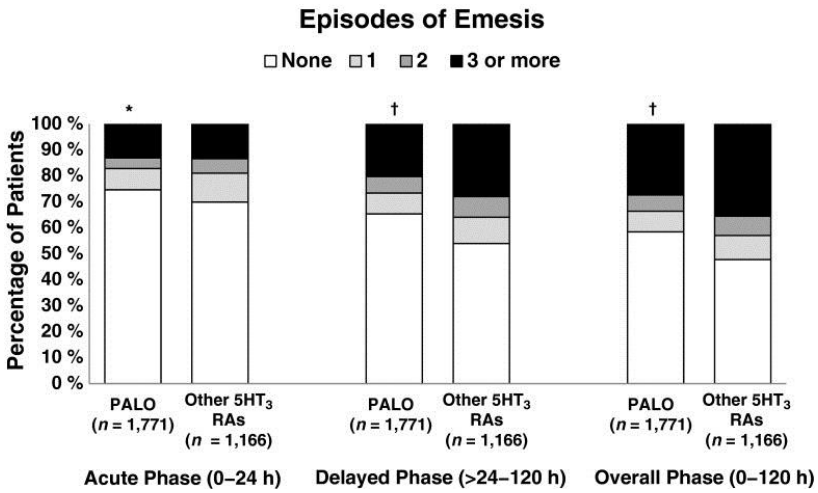
- Olanzapine

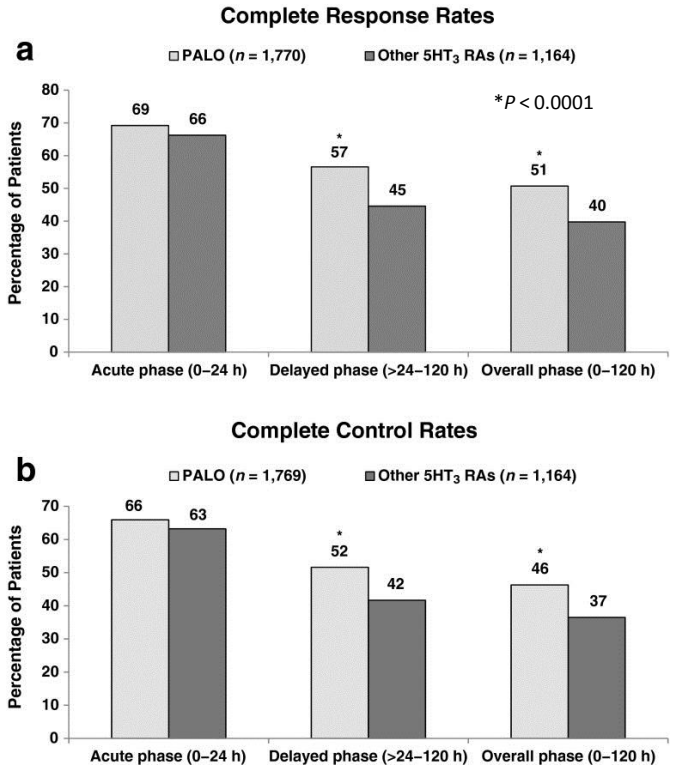
- Palonosetron
- Subcutaneous granisetron (APF530)

- NEPA (Netupitant/Palonosetron)
- Rolapitant

Palonosetron

- 2nd generation 5HT3 antagonist
  - Longer half-life
  - Stronger binding affinity to the receptor
  - Low risk of QTc prolongation
- Pooled analysis of 4 phase III RCTs

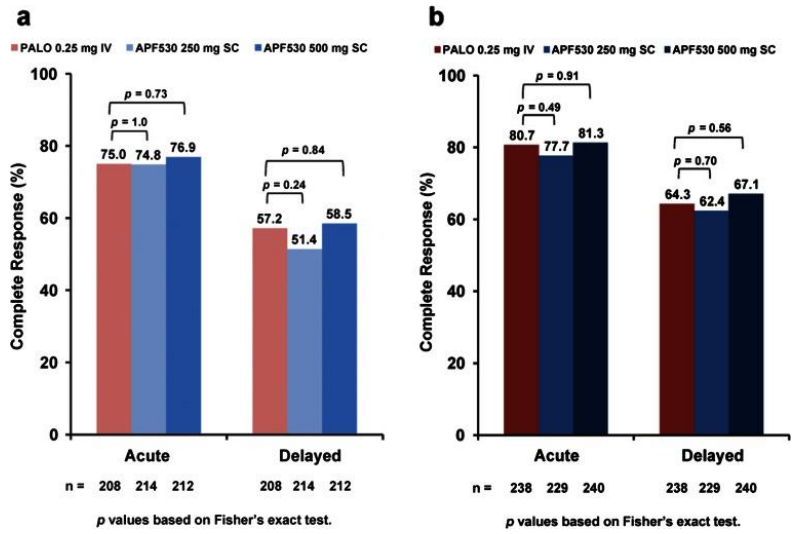


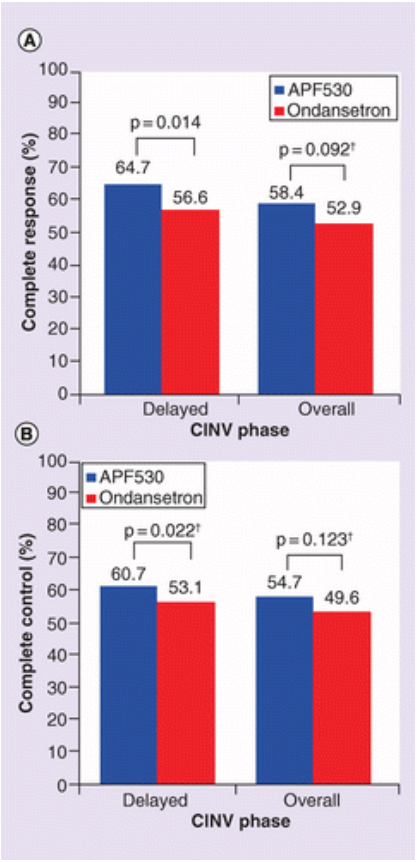


Schwartzberg L, et al. Support Care Cancer. 2014;22(2):469-77.

APF530 (Sustol©)

- Extended release, subcutaneous granisetron
- Provides sustained release of therapeutic concentrations of granisetron for ~5 days
  - 250mg SC dose = 5mg IV dose
  - 500mg SC dose = 10mg IV dose





Schnadig ID, et al. Future Oncol. 2016;12(12):1469-81.
Raftopoulos H, et al. Support Care Cancer. 2015;23(3):723-32.

NEPA (Akynzeo©)

- Netupitant 300mg/ Palonosetron 0.5mg
- Greater convenience vs cost

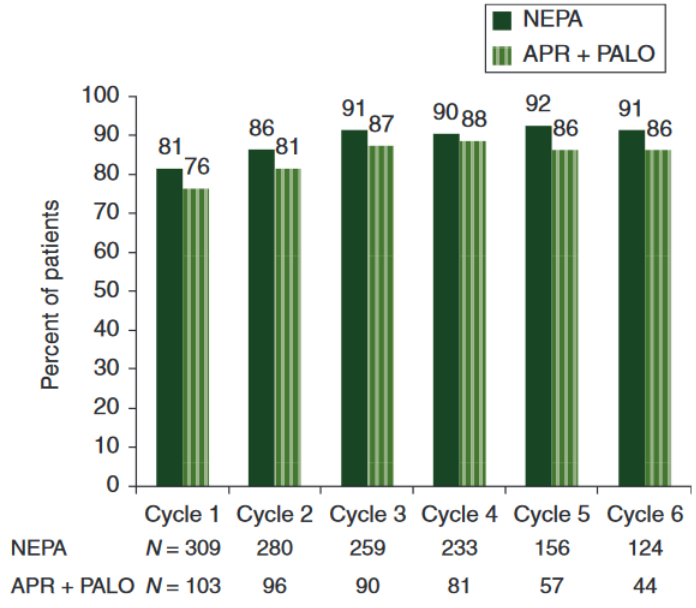
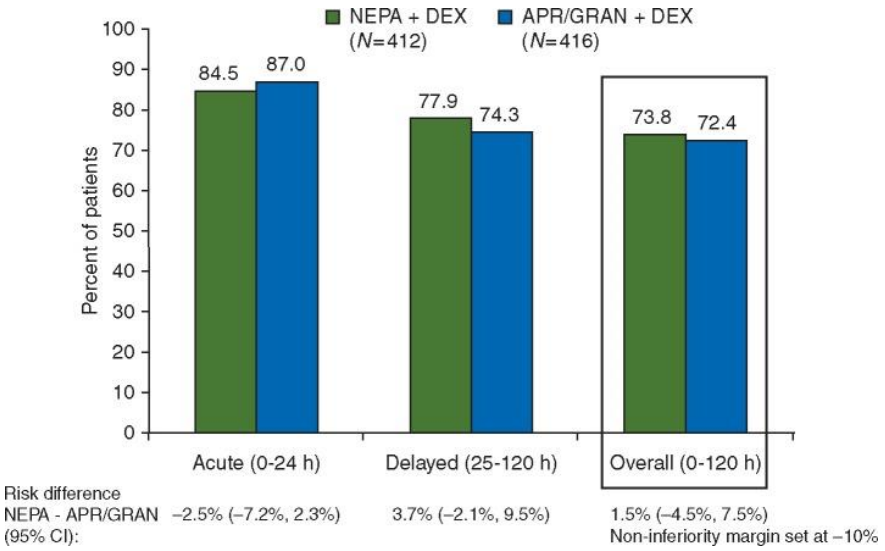


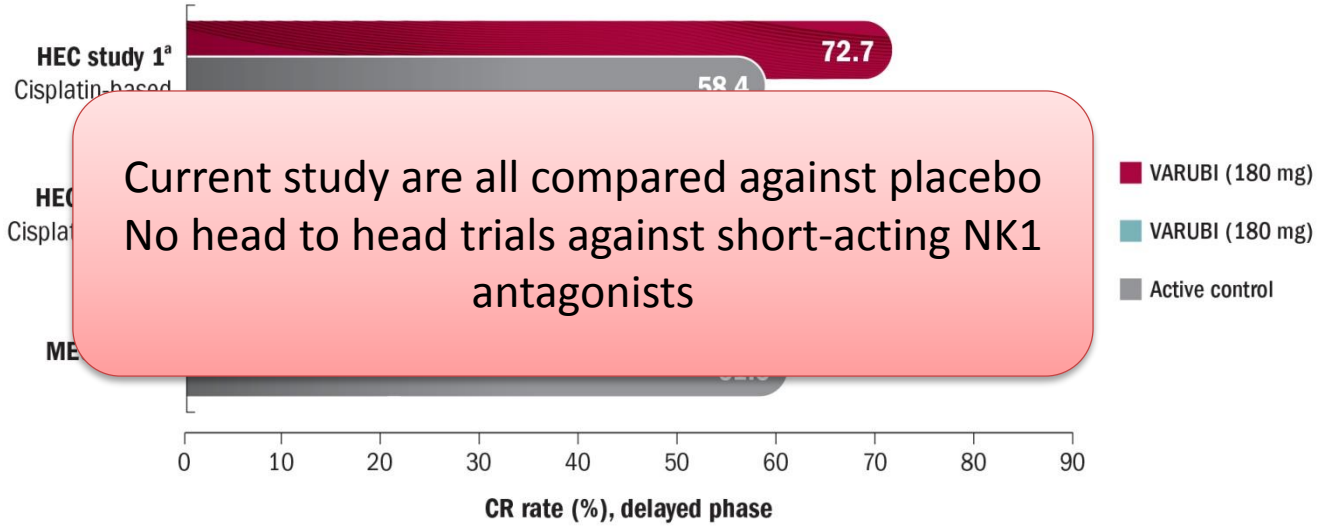
Figure 2. Primary analysis: complete response (no emesis, no rescue medication) (overall 0–120 h). Full analysis population.



Gralla RJ, et al. Ann Oncol. 2014;25(7):1333-9.
Zhang L, et al. Ann Oncol. 2018;29(2):452-458.

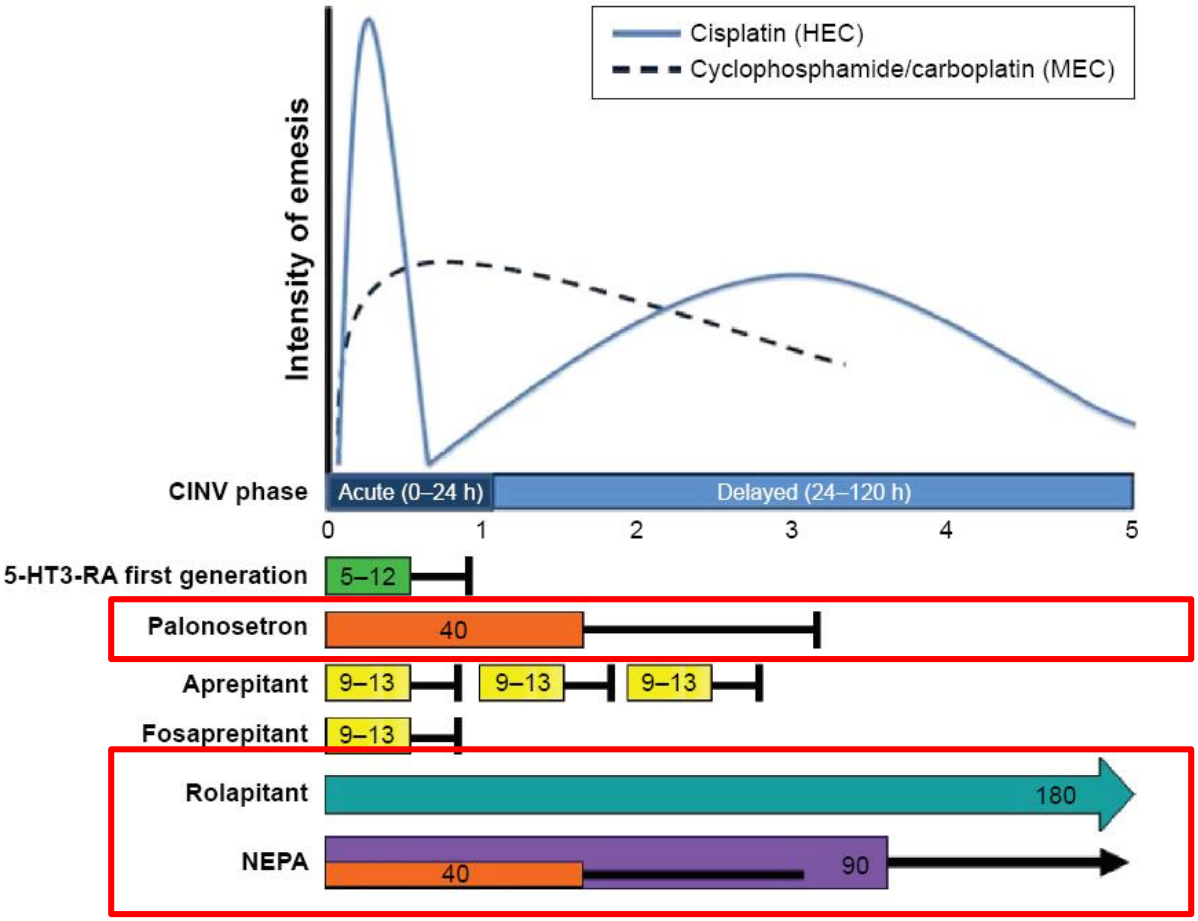
Rolapitant (Varubi©)

- Oral, long acting NK1 antagonist
  - Half-life ~7 days
- Does not inhibit or induce CYP3A4



Tesaro, Inc. https://www.varubirx.com/en/efficacy. Accessed on: 22 July 2018.

Recent Developments



Lorusso V. Ther Clin Risk Manag. 2016;12:917-25.

Moderate Emetic Risk

NCCN 2018	ASCO 2017	MASCC/ESMO 2016
5HT3 DEX + Cont D2-3	For Carboplatin AUC ≥ 4 NK1 5HT3 DEX + Cont D2-3	For Carboplatin
PALO DEX OLA + Cont D2-4	For other agents 5HT3 DEX + Cont D2-3*	

*only for patients who are treated agents that are known to cause delayed nausea and vomiting

Low Emetic Risk

NCCN 2018	ASCO 2017	MASCC/ESMO 2016
5HT3 **OR** DEX **OR** DOPA	5HT3 **OR** DEX	5HT3 **OR** DEX **OR** DOPA

Non-pharmacological managment

- Take small, frequent meals. Avoid heavy meals.
- Avoid greasy, spicy, very sweet or salty food and food with strong flavors or smells.
- Sip small amounts of fluid often instead of trying to drink a full glass at one time.
- Avoid caffeinated beverages.
- Avoid lying flat for 2 hours after eating.

Anticipatory nausea/vomiting

- Prevention is key
  - Use optimal anti-emetic therapy during every cycle of treatment
- Behavioral therapy
  - Relaxation/systematic desensitization
  - Hypnosis/guided imagery
  - Music therapy
- Acupuncture/acupressure
- Consider anxiolytic therapy
  - PO alprazolam 0.5-1mg/ lorazepam 0.5-2mg on the night before treatment and then 1-2 hours before chemotherapy begins

Case 2 (Ms ABC)

- 35 y/o Chinese lady
- No known drug allergies
- Single; no children
- Social History
  - Ex smoker 10 pack years
  - Non-drinker
- Medical History
  - Amenorrhea
  - Diabetes

Case 2

- Presenting complain
  - Unable to get out of bed
  - A/w 2/7 Hx of LL weakness and ARU
  - Lax anal tone
- MRI Brain:
  - L frontal lobe lesions mass effect with rim enhancing cystic changes
  - Periventricular/subependymal involvement
  - Crossing midline via corpus callosum and with suspicious extenson to the thickened pituitary stalk
- Elevated betaHCG levels

Case 2

- Diagnosis: intracranial germ cell tumour with spinal mets

- Oncologic treatment plan:
  - BEP (Bleomycin, Etoposide, Cisplatin)

Drug	Dose	Days
Bleomycin	15mg	D1
Etoposide	100mg/m2	D1 - D5
Cisplatin	20mg/m2	D1 - D5

Case 2

- What are the risk factors for CINV in Ms ABC's case?
- What would be an appropriate antiemetic regimen for her?
- On Day 4 of treatment, patient had breakthrough vomiting. What would be your recommendation?

Case 2 (Ms ABC)

- 35 y/o Chinese lady
- Single; no children
- Social History
  - Ex smoker 10 pack years
  - Non-drinker

Drug	Dose	Days
Bleomycin	15mg	D1
Etoposide	100mg/m2	D1 - D5
Cisplatin	20mg/m2	D1 - D5

Multiday Cisplatin Chemotherapy

- No clear recommendations by guidelines

NCCN 2018	ASCO 2017	MASCC/ESMO 2016
Recommends NK1 antagonist, 5HT3 antagonist and dexamethasone for HEC. Antiemetic regimen should be individualized.	NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone. Patients should be offered antiemetics on each day of treatment and for 2 days after completion of the antineoplastic regimen.	5-HT3 RA plus dexamethasone plus aprepitant for the prevention of acute nausea and vomiting and dexamethasone for delayed nausea and vomiting.

Multiday Cisplatin Chemotherapy

- PO Aprepitant 125mg (D1), 80mg (D2-3)
- IV Granisetron 3mg X 5/7
- PO Dexamethasone 4mg BD X 5/7

- Post-chemo, patient continued on another 2/7 of dexamethasone, followed by short taper

Breakthrough treatment

BREAKTHROUGH TREATMENT FOR CHEMOTHERAPY-INDUCED NAUSEA/VOMITING[h,y]

Any nausea/ vomiting

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen.
(order does not imply preference)

- Atypical antipsychotic:[j]
  - Olanzapine 5–10 mg PO daily (category 1)[z,aa]
- Benzodiazepine:[j]
  - Lorazepam 0.5–2 mg PO/SL/IV every 6 h[aa]
- Cannabinoid:[j]
  - Dronabinol capsules 5–10 mg, or dronabinol oral solution 2.1-4.2 mg/m², PO 3-4 times daily[bb]
  - Nabilone 1–2 mg PO BID
- Other:
  - Haloperidol 0.5–2 mg PO/IV every 4–6 h[j]
  - Metoclopramide 10–20 mg PO/IV every 4–6 h[j]
  - Scopolamine 1.5 mg transdermal patch 1 patch every 72 h
- Phenothiazine:[j]
  - Prochlorperazine 25 mg supp PR every 12 h or 10 mg PO/IV every 6 h[j]
  - Promethazine 25 mg supp PR every 6 h or 12.5–25 mg PO/IV (central line only) every 4–6 h[j]
- 5-HT3 RA:[j]
  - Dolasetron 100 mg PO daily
  - Granisetron 1–2 mg PO daily or 1 mg PO BID or 0.01 mg/kg (maximum 1 mg) IV daily or 3.1 mg/24-h transdermal patch every 7 days
  - Ondansetron 16–24 mg PO daily or 8-16 mg IV
- Steroid:[j]
  - Dexamethasone 12 mg PO/IV daily

RESPONSE

SUBSEQUENT CYCLES

Nausea and vomiting controlled → Continue breakthrough medications, on a schedule, not PRN

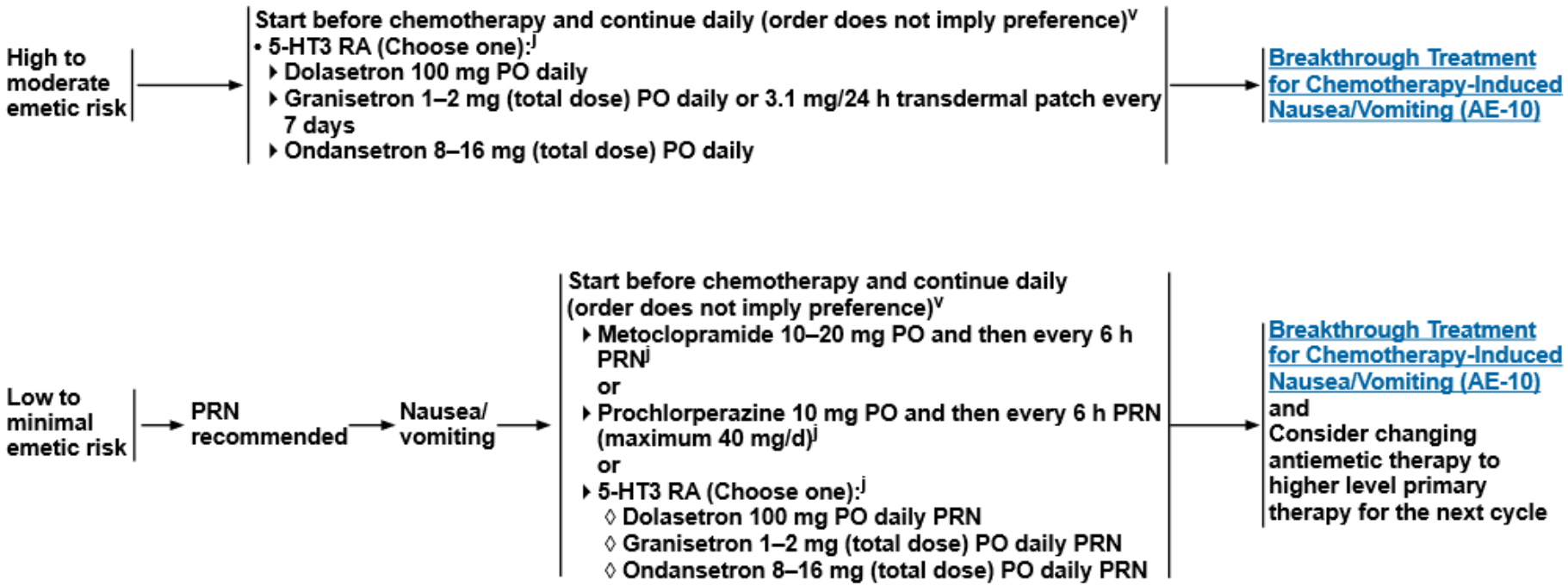
Nausea and/ or vomiting uncontrolled → Re-evaluate and consider dose adjustments and/ or sequentially add one agent from a different drug class

Consider changing antiemetic therapy to higher level primary treatment for next cycle

[z]When not used as part of the acute and delayed emesis prevention regimen. Navari RM, Nagy CK, Gray SE. The use of olanzapine versus metoclopramide for the treatment of breakthrough chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy. Support Care Cancer 2013;21:1655-1663.

[aa]For olanzapine-containing regimens, only use PO lorazepam. See Principles of Emesis Control for the Cancer Patient (AE-1).

Oral chemotherapy – Emesis prevention



NCCN Guidelines 3.2018, Anti-emesis

The END

- Reference guidelines
  - National Comprehensive Cancer Network. Anti-emesis (Version 3.2018). 22 July 2018. http://www.nccn.org/professionals/physician_gls/pdf/anti-emesis.pdf
  - 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.
  - Roila F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol. 2016;27(suppl 5):v119-v133.