AN UPDATE ON CHEMOTHERAPY INDUCED NAUSEA & VOMITING (CINV)

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Faculty/Presenter Disclosure

- **Faculty:** Andrew Knight, MD

- **Relationships with financial sponsors:**

- No financial relationships or conflicts of interest to disclose.

Learning Objectives

- At the conclusion of this presentation, participants will become knowledgeable regarding:

- The role of anti-emetics in the administration of chemotherapy
- How to apply the data presented regarding the relevant receptors that are targeted
- The relevant guidelines for the use of anti-emetics
- Drug-drug interactions including which classes of medications are involved & what actions can mitigate toxicities

Historical Context

- Nitrogen mustard (HN-2) was the first cancer chemotherapy drug approved by the US Food and Drug Administration (FDA) about [70] years ago (Van Laar, Desai, & Jatoi, 2015).

- An early clinical report documented its toxicity:

"The most important toxic effect of HN2 is the gastrointestinal disturbance that occurs in almost all patients. Nausea, usually with vomiting, begins one to three hours after injection and lasts for two to three hours, occasionally until the next day…. In our hands rather heavy sedation has been the most effective means of controlling the nausea and vomiting. Ordinarily we have used 0.2 gm of sodium amytal…. Sleep may be interrupted by nausea and even vomiting but some rest is obtained…."
(Wintrobe & Huguley, 1948)

Classification of CINV:

Acute: < 24 hours post chemotherapy, reaches maximum intensity at 5-6 hrs

Delayed: > 24 hours post chemotherapy, may persist 5-7 days, reaches maximum intensity at 48-72 hrs

Anticipatory: conditioned response occurs prior to chemotherapy, certain triggers, usually prior experience with CINV (Janelsins et al., 2013)

- Main objective to completely prevent rather than treat CINV
- Achievable in majority of patients even receiving highly emetogenic chemotherapy (Hesketh, 2018)

Estimating Risk of CINV

- Most important factor intrinsic emetogenicity of any particular agent
- Multi-drug regimens

- Chemotherapy agents divided into four categories based upon risk of emesis (in absence of antiemetic prophylaxis):
  - Highly emetogenic – >90 percent risk of emesis (HEC)
  - Moderately emetogenic – >30 to 90 percent risk of emesis (MEC)
  - Low emetic risk – 10 to 30 percent risk of emesis (LEC)
  - Minimal emetic risk – <10 percent risk of emesis (MiEC)

- Antiemetic regimens selected based on risk (Hesketh, 2018)

Committee I (2/5): Emetic Risk Groups – Adults – Single IV Agents

HIGH	Anthracycline/cyclophosphamide combination* Carmustine Cisplatin Cyclophosphamide ≥ 1500 mg/m² Dacarbazine Mechlorethamine Streptozocin		
MODERATE	Alemtuzumab Azacitidine Bendamustine Carboplatin Clofarabine Cyclophosphamide < 1500 mg/m² Cytarabine > 1000 mg/m²	Daunorubicin Doxorubicin Epirubicin Idarubicin Ifosfamide Irinotecan	Oxaliplatin Romidepsin Temozolomide** Thiotepa Trabectedin

* The combination of an anthracycline and cyclophosphamide in patients with breast cancer should be considered highly emetogenic.
** No direct evidence found for temozolomide IV. Classification is based on oral temozolomide, since all sources indicate a similar safety profile.

(MASCC, 2016)

Committee I (3/5): Emetic Risk Groups – Adults – Single IV Agents

LOW	Aflibercept Belinostat Blinatumomab Bortezomib Brentuximab Cabazitaxel Carfilzomib Catumaxumab Cetuximab Cytarabine ≤1000 mg/m² Docetaxel	Eribulin Etoposide 5-Fluorouracil Gemcitabine Ipilimumab Ixabepilone Methotrexate Mitomycin Mitoxantrone Nab- paclitaxel Paclitaxel	Panitumumab Pemetrexed Pegylated liposomal doxorubicin Pertuzumab Temsirolimus Topotecan Trastuzumab-emtansine Vinflunine

(MASCC, 2016)

Committee I (4/5): Emetic Risk Groups – Adults – Single IV Agents

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

(MASCC, 2016)

Individual Patient Characteristics

- Younger age (<50)
- Female
- Emesis during pregnancy
- Minimal or no previous alcohol exposure
- History of motion sickness
- Previous chemotherapy & CINV

- Above not considered in selection of prophylactic anti-emetic regimens (Hesketh, 2018)

CINV – consequences when poorly managed:

- Anxiety & depression
- Impaired function
- Diminished QOL
- Fear of CINV
- Reduced adherence to chemotherapy
- Increased resource utilization (hospitalization, etc)
- Abandonment of treatment (Janelsins et al., 2013)

CINV: Receptors & Pathways

- Complex multifactorial process involving receptors & neurotransmitters in both CNS & GI tract
- Main receptors targeted by current anti-emetic regimens:

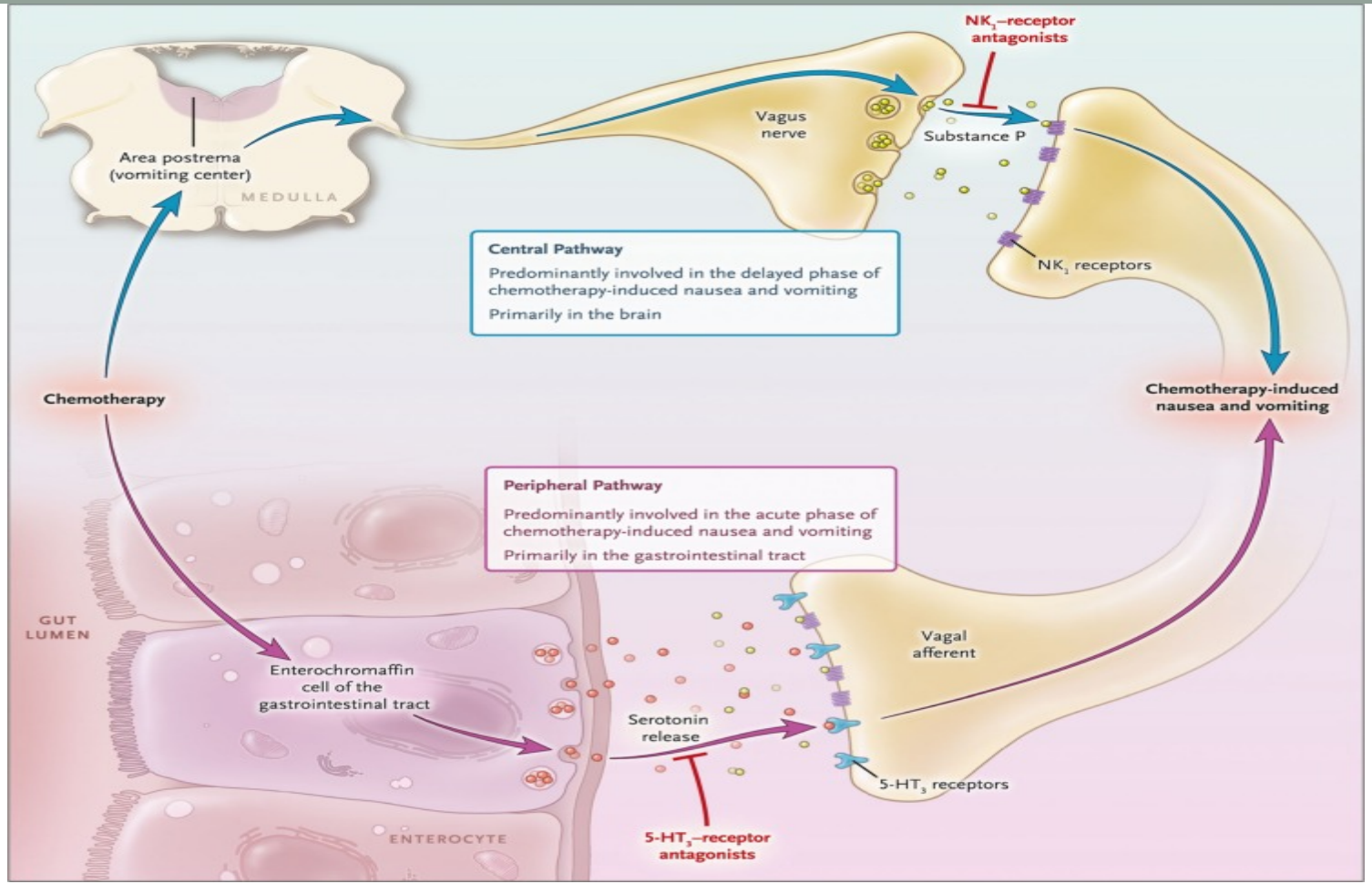
Receptor	5HT3	NK-1	D2
Neurotransmitter	Serotonin	Substance P	Dopamine

(Aapro, 2018)

CINV: Receptors & Pathways

- 2 distinct mechanisms:
- Peripheral pathway (Serotonin) activated in GI tract in 1st 24hr post chemotherapy (acute CINV)
  - damaged enterochromaffin cells in gut release 5HT
- Central pathway (Substance P) primarily in CNS (delayed CINV)
  - (acute CINV may also occur via central pathway)

(Aapro, 2018)



(Navari & Aapro, 2016)

CINV

- Acute
- First 24 hrs
- Peripheral pathway
- Serotonin / 5HT-3

- Delayed
- 24-120 hrs
- Central pathway
- Substance P / NK-1

5HT3 Antagonists – 1st Generation

- Ondansetron (t½ = 4hr); Granisetron (t½ = 9hr); [Dolasetron]
- Equally effective, single dose schedule = multidose
- Therapeutic plateau, dose escalation not improve outcome
- Efficacy enhanced when combined with glucocorticoids
- Prolonged QT – class effect of 1st generation
- Main AEs headache, constipation
- Potential for serotonin syndrome when combined with other agents (Hesketh, 2018)

5HT3 Antagonists – 2nd Generation

- Palonosetron (t½ > 40hr), 30-100 greater receptor affinity
- QT prolongation not reported
- Superior to 1st generation agents when combined with glucocorticoid in preventing delayed CINV (Hesketh, 2018)

- Internalizes 5HT3 receptor
- Prevention of “crosstalk” with NK-1 receptor (Aapro, 2018)

NK-1 Antagonists

- Better prevention of both acute & delayed CINV in patients receiving both MEC (containing carboplatin) & HEC when combined with 5HT3 antagonist & glucocorticoid
- Aprepitant & Netupitant: moderate CYP 3A4 inhibitors – require dose reduction in glucocorticoid (if used as antiemetic) (Hesketh, 2018)

- Netupitant metabolized through CYP 3A4 – potential for significant drug interactions – caution with CYP 3A4 inhibitors & avoid strong inducers (Purdue Pharma, 2017)

Netupitant/Palonosetron

- Fixed dose 300mg / 0.5mg, respective t½ of 96 & 44 hrs
- Single dose Day 1, HEC & MEC (Carboplatin)
- Caution: combining with other agents that prolong QT & raise serotonin levels
- Docetaxol & Etoposide (both metabolized through 3A4) showed increase of 35% & 28% in respective AUC
- 2-fold increase in dexamethasone AUC → 50% dose reduction (Purdue Pharma, 2017)

Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting

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ABSTRACT

BACKGROUND

We examined the efficacy of olanzapine for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy.

METHODS

In a randomized, double-blind, phase 3 trial, we compared olanzapine with placebo, in combination with dexamethasone, aprepitant or fosaprepitant, and a 5-hydroxytryptamine type 3–receptor antagonist, in patients with no previous chemotherapy who were receiving cisplatin (≥70 mg per square meter of body-surface area) or cyclophosphamide–doxorubicin. The doses of the three concomitant drugs administered before and after chemotherapy were similar in the two groups. The two groups received either 10 mg of olanzapine orally or matching placebo daily on days 1 through 4. Nausea prevention was the primary end point; a complete response (no emesis and no use of rescue medication) was a secondary end point.

RESULTS

In the analysis, we included 380 patients who could be evaluated (192 assigned to olanzapine, and 188 to placebo). The proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine than with placebo in the first 24 hours after chemotherapy (74% vs. 45%, P=0.002), the period from 25 to 120 hours after chemotherapy (42% vs. 25%, P=0.002), and the overall 120-hour period (37% vs. 22%, P=0.002). The complete-response rate was also significantly increased with olanzapine during the three periods: 86% versus 65% (P<0.001), 67% versus 52% (P=0.007), and 64% versus 41% (P<0.001), respectively. Although there were no grade 5 toxic effects, some patients receiving olanzapine had increased sedation (severe in 5%) on day 2.

CONCLUSIONS

Olanzapine, as compared with placebo, significantly improved nausea prevention, as well as the complete-response rate, among previously untreated patients who were receiving highly emetogenic chemotherapy. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT02116530.)

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(Navari et al., 2016)

Olanzepine

- Blocks following receptors:
- Dopamine (D1-4)
- Serotonin (5HT2a, 5HT2c, 5HT3, 5HT6)
- Muscarinic (M1)
- Histamine (H1)
- Adrenergic (α_1)

- Anti-emetic activity primarily through D2, 5HT2 & 5HT3 (Navari et al., 2016)

CancerCareOntario – Antiemetic Report – October 2013

Antiemetic Recommendations for Highly Emetogenic Chemotherapy (HEC)

- Aprepitant 125 mg po pre-chemotherapy on Day 1 then 80 mg po od on Days 2 – 3 **OR**
- Fosaprepitant 150 mg IV pre-chemotherapy on Day 1
  AND
- Granisetron 2 mg po or 1 mg IV pre-chemotherapy on Day 1 **OR**
- Ondansetron 8 mg po bid or 8 mg IV on Day 1 starting pre-chemotherapy **OR**
- Dolasetron 100 mg po pre-chemotherapy on Day 1 **OR**
- Palonosetron 0.25 mg IV pre-chemotherapy on Day 1
  AND
- Dexamethasone 12 mg PO or 10 mg IV pre-chemotherapy on Day 1 then 8 mg po or 10 mg IV on Days 2 – 3 or 4

Antiemetic Recommendations for Moderately Emetogenic Chemotherapy (MEC)

- Granisetron 2 mg po or 1 mg IV pre-chemotherapy on Day 1 **OR**
- Ondansetron 8 mg po bid or 8 mg IV on Day 1 starting pre-chemotherapy **OR**
- Dolasetron 100 mg po pre-chemotherapy on Day 1 **OR**
- Palonosetron 0.5 mg po or 0.25 mg IV pre-chemotherapy on Day 1
  AND
- Dexamethasone 8 mg po or 10 mg IV pre-chemotherapy on Day 1

OPTIONAL addition in cases of uncontrolled emesis despite above

- Aprepitant 125 mg po pre-chemotherapy on Day 1 then 80 mg po od on Days 2 – 3 **OR**
- fosaprepitant 150 mg IV pre-chemotherapy on Day 1

Antiemetic Recommendations for Low Emetic Risk Chemotherapy (Low)

- Dexamethasone 8 mg po or 10 mg IV pre-chemotherapy on Day 1

Antiemetic Recommendations for Minimal Emetic Risk Chemotherapy (Minimal)

- Nothing routinely; may give a dopamine receptor antagonist (e.g. prochlorperazine 10 mg po) pre-chemotherapy on Day 1

(Cancer Care Ontario, 2013)

ASCO 2017 – Summary of Acute & Delayed CINV Prevention

	Emetic Risk Group	Risk%	Acute CINV Day 1	Delayed CINV Day 2&3	Delayed CINV Day 4
HEC	Non-AC HEC	>90	5HT3 + NK1 + DEX + OLA	NK1 + DEX + OLA	DEX + OLA
	AC HEC			NK1 + OLA	OLA
MEC	MEC (Carboplatin AUC> 4)	30-90	5HT3 + NK1 + DEX	-	-
	MEC (delayed CINV: Cyclo, Doxo, Oxali)		5HT3 + DEX	DEX	-
	MEC Others (including Carboplatin AUC< 4			-	-
LEC	Low	10-30	5HT3 or DEX	-	-
MiEC	Minimal	<10	-	-	-

(Hesketh et al., 2017)

ASCO 2017 – Clinical Practice Guideline Update

- Adjunctives: Lorazepam
- Cannabinoids: insufficient evidence for medicinal marijuana (MM) or MM replacing Nabilone / [Dronabinol]
- Complementary: insufficient evidence for ginger, acupuncture, other
- Breakthrough: add Olanzepine

(Hesketh et al., 2017)

ACUTE Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	5-HT_3 + DEX + NK_1
High AC	5-HT_3 + DEX + NK_1
Carboplatin	5-HT_3 + DEX + NK_1
Moderate (other than carboplatin)	5-HT_3 + DEX
Low	5-HT_3 or DEX or DOP
Minimal	No routine prophylaxis

5-HT_3 = serotonin$_3$ receptor antagonist

DEX = DEXAMETHASONE

NK_1 = neurokinin$_1$ receptor antagonist such as APREPITANT or FOSAPREPITANT or ROLAPITANT or NEPA (combination of netupitant and palonosetron)

DOP = dopamine receptor antagonist

NOTE: If the NK_1 receptor antagonist is not available for AC chemotherapy, palonosetron is the preferred 5-HT_3 receptor antagonist.

(MASCC, 2016)

DELAYED Nausea and Vomiting: SUMMARY

EMETIC RISK GROUP	ANTIEMETICS
High Non-AC	**DEX** or (if APR 125mg for acute: (**MCP** + **DEX**) or (**APR** + **DEX**))
High AC	None or (if APR 125mg for acute: **DEX** or **APR**)
Carboplatin	None or (if APR 125mg for acute: **APR**)
Oxaliplatin, or anthracycline, or cyclophosphamide	**DEX** can be considered
Moderate (other)	No routine prophylaxis
Low and Minimal	No routine prophylaxis

DEX = DEXAMETHASONE | **MCP** = METOCLOPRAMIDE | **APR** = APREPITANT

(MASCC, 2016)

Prolonged QT

- Baseline EKG, correct QT for HR (QTc)

- Many QT prolonging drugs metabolized via CYP 3A4
- Caution with use of strong 3A4 inhibitors

- ICH E14 guidelines (ICH, 2015)

- Prochlorperazine (↑QT) (Yapp & Camm, 2003)

Prolonged QT

Class	Drug	Cardiotoxicity	ICH E14 Compliant	
5HT3	Ondansetron	↑QT	Yes	Dose dependant ↑QT
	Granisetron	EKG Δs, arrhythmias	No	Limited data
	(Granisetron TD)		Yes	No ↑QT
	Palonosetron		Yes	No ↑QT
NK-1	Aprepitant		No	Unknown
	Fosaprepitant		Yes	No ↑QT
	Netupitant		Yes	No ↑QT
D2	Metoclopramide	↑QT	No	
	Haloperidol	↑QT & TdP	No	
	Olanzepine	↑QT	No	↑risk in combination with other anti-psychotics

(table adapted from Barni, Petrelli, & Cabiddu, 2016)

Serotonin Syndrome (Toxicity)

- Presentation variable, mild to life threatening
- Altered mental status:

  agitation, anxiety, disorientation, excitation, restlessness
- Neuromuscular hyperactivity:

  tremours, clonus, hyper-reflexia, rigidity, Babinski, akathisia
- Autonomic hyperactivity:

  hypertension, tachycardia, arrhythmias, tachypnea, hyperthermia, mydriasis, flushing, dry mouth, vomiting, diarrhea, diaphoresis, shivering

(Volpi-Abadie, Kaye, & Kaye, 2013)

Serotonin Syndrome (Toxicity)

- Number of drug classes can raise serotonin levels:
- 5HT3s
- SSRIs, SNRIs, TCAs, MAOIs
- Tramadol, Fentanyl, Methadone, Dextromethorphan, Meperidine
- Atypical antipsychotics – (may precipitate, also used to treat)

- Potential for CYP 2D6 & 3A4 inhibitors

(Volpi-Abadie et al., 2013)

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