

Management of Chemotherapy Induced Nausea/Vomiting(CINV) in Adult Cancer Patients

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Goals and Objectives:

- Describe different type of CINV- acute vs. delayed and anticipatory emesis.
- Describe patient's risk factors for developing CINV.
- Discuss potential emetogenicity of chemotherapy regimens.
- Discuss pathophysiology of CINV & Neurotransmitters involved
- Recognize role of 5HT3-RA & NK1-RA in pharmacologic approaches to management of CINV.
- Recommend optimal antiemetic prophylaxis based on overall emesis risk factors & Recommendations in the NCCN Guidelines for Antiemesis.

Audience Question# 1

Which one is the most common feared side effect of chemotherapy?

1- Immune suppression

2- Fatigue

3- Febrile Neutropenia

4- Vomiting

Chemotherapy Induced Nausea Vomiting(CINV)

Few side effects of cancer treatment are more feared by the patient than nausea and vomiting.

- Three phases of emesis include: nausea, retching, and Vomiting.
- Goal is Prevention.

Types of Emesis

- Three distinct types of CINV have been defined: **acute, delayed, and anticipatory.**
- Recognizing the differences between these types of CINV has important implications for both prevention and management CINV.

Acute Emesis

- It is the most widely studied form of CINV.
- In the absence of an effective prophylaxis anti-emetic regimen:
- It occurs during the first 24 hours after chemotherapy
- The onset is usually within 1-2 hours of Chemotherapy.
- It peaks in the first 4-6 hours.
- Most easily prevented and treated with current anti-emetic drugs.

Delayed Emesis

- Any emesis occurring after 24 hours post chemotherapy.
- Underlying Pathophysiology not well understood.
- Best example is high dose cisplatin, but can occur with other agents such as cyclophosphamide, carboplatin, anthracyclines, and Ifosfamide.
- It peaks at 48-72 hours in the absence of effective prophylaxis.
- Delayed emesis is less controlled with current anti-emetics.
- Patients who have complete control of acute emesis are less predisposed to delayed symptoms.

Anticipatory Emesis

- A conditioned reflex in patients who have developed significant nausea and vomiting during previous cycles.
- Very important to provide maximal control of emesis earlier in treatment.
- Usually occurs 24 hours prior to treatment.
- Susceptible population: younger adults, patients receiving chemotherapy treatment for longer periods of time.

Risk Factors for Developing CINV

- Patient Risk Factors(may or may not increase overall emesis risk)
- Regimen Risk Factors

Overall Emesis Risk= Patient's risk factors + Regimen risk factors

Audience Response Question #2

JD is a 40-year old depressed woman who is diagnosed recently with extensive stage small cell lung cancer. She is a social drinker, stopped smoking 15 years ago. Her PMH is significant for morning sickness with her 2 pregnancies and motion sickness. Her oncologist wishes to use cisplatin 75mg/m² IV D1, etoposide 100 mg/m² IV D1-3 of every 21 days times 6 cycles as her chemotherapy treatment.

what are JD's specific risk factors for developing N/V?

- A- female
- B- Age
- C- History of morning Sickness
- D- History of motion sickness

Patient specific risk factors for developing CINV

- Anxiety, expectation of nausea
- Women>men
- Psychosocial factors(anxiety, depression, etc.)
- Younger age (i.e., <50 y/o)
- History of motion sickness
- Pregnancy-induced nausea/vomiting
- History of moderate alcohol use (protective)
- Extent of disease(stage)
- Anti-emetics inconsistent with guidelines
- Prior chemotherapy and degree of anti-emetic control

Regimen Specific Risk Factors

- Dose and Schedule of regimen
- Single-agent chemotherapy emetogenic categories:
 - High
 - Moderate
 - Low
 - Minimal
- For multi-drug regimens: the drug that has the highest level of emetogenicity determines the regimen's emetic risk level.
- No longer “calculate” emetogenicity of multiple drug regimens

EMETOGENIC POTENTIAL OF ANTICANCER AGENTS

It is based on the proportion of patients who experience emesis in the absence of effective antiemetic prophylaxis.

- High Emetic risk →→→ over 90 % frequency of emesis
- Moderate Emetic Risk →→→ 30-90% frequency of emesis
- Low Emetic Risk →→→ 10-30 % frequency of emesis
- Minimal Emetic Risk → →→ less than 10% frequency of emesis

Emetogenic Potential of IV Anticancer Agents

in the absence of effective antiemetic prophylaxis

Highly Emetogenic- >90% incidence in acute and delayed emesis

- Cyclophosphamide/doxorubicin combination
- Cisplatin
- Higher doses of specific chemotherapy agents (e.g. Carboplatin AUC= 4 & >4)

Emetogenic Potential of IV Anticancer Agents

in the absence of effective antiemetic prophylaxis

Moderately Emetogenic- 30-90% risk of acute and delayed emesis

- Carboplatin, Oxaliplatin
- Anthracyclines (relatively lower doses)
 - Nitrogen mustards (e.g. Bendamustine, Ifosfamide, Cyclophosphamide, Irinotecan)

Emetogenic Potential of IV Anticancer Agents

in the absence of effective antiemetic prophylaxis

Low Emetogenic- 10-30% risk of acute emesis

- Antimicrotubules (e.g., Taxanes)
- Antimetabolites & antifolates (e.g. Fluorouracil, Methotrexate, Pemetrexed)

Emetogenic Potential of IV Anticancer Agents

in the absence of effective antiemetic prophylaxis

Minimally Emetogenic- <10% risk of acute emesis
– Monoclonal antibodies, Vinca Alkaloids

See NCCN Guidelines for Antiemesis (available at: www.nccn.org) for complete list

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS

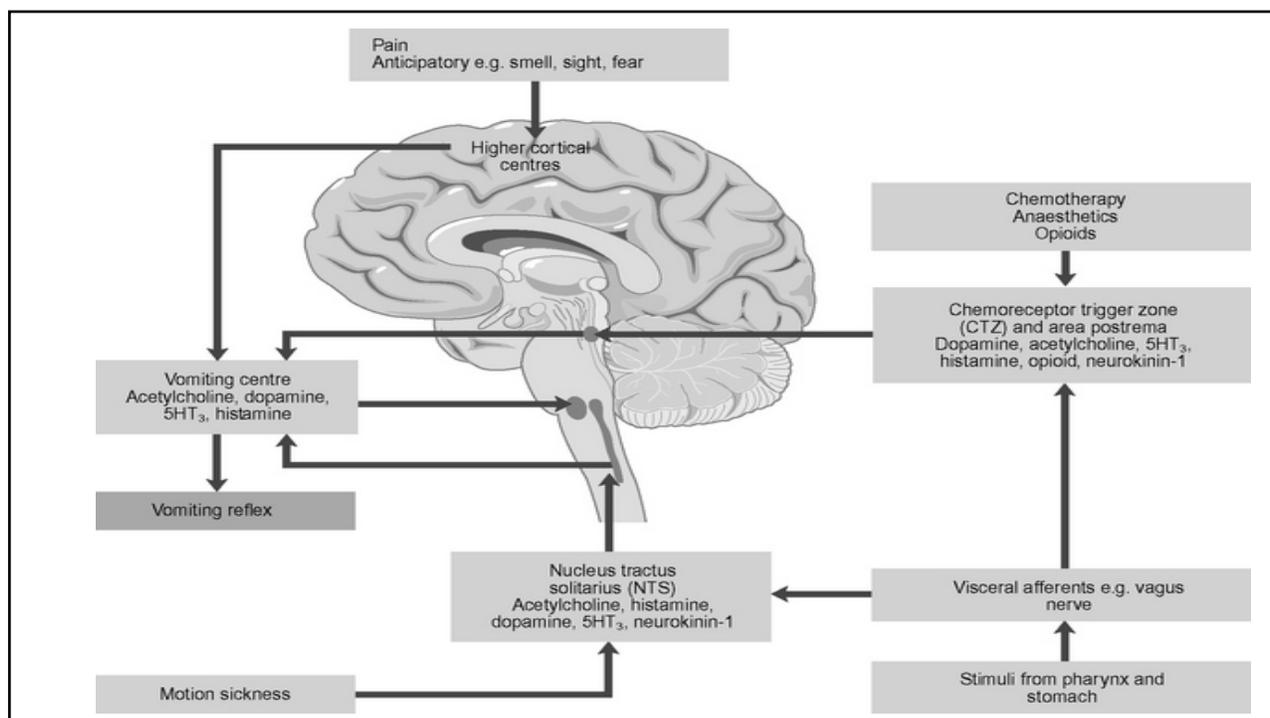
Moderate to high emetic risk($\geq 30\%$ frequency of emesis):

- Cytotoxic chemotherapy- Cyclophosphamide ≥ 100 mg/m²/d, Temozolomide >75 mg/m²/d
- Crizotinib
- PARP inhibitors- Olaparib, Rucaparib, Niraparib

Minimal to low($<30\%$ frequency of emesis) :

- Capecitabine
- Temozolomide <75 mg/m²/d
- “-nibs” – Gefitinib, Afatinib, Sunitinib, Regorafenib
- CDK4/6 inhibitors- Palbociclib, Ribociclib, Abemaciclib

See NCCN Guidelines for Antiemesis (available at: www.nccn.org) for complete list



Pathophysiology of CINV

- Vomiting is triggered by afferent impulses to the vomiting center, a nucleus of cells in the medulla.
- Impulses are received from sensory centers, such as the chemoreceptor trigger zone (CTZ), cerebral cortex, and visceral afferents from the pharynx and GI tract.
- When excited, afferent impulses are integrated by the vomiting center, resulting in efferent impulses to the salivation center, respiratory center, and the pharyngeal, GI, and abdominal muscles, leading to vomiting.

Pathophysiology of Nausea/Vomiting

- The vomiting reflex is triggered by afferent impulses to the vomiting center from vagus nerve terminals in the wall of the small bowel, the chemoreceptor trigger zone, or the cerebral cortex.
- The act of vomiting occurs when efferent impulses are sent to a number of organs and tissues such as the abdominal muscles, salivary glands, cranial nerves, and respiratory center

Neurotransmitters Involved in CINV

- Many neurotransmitters are potentially involved in CINV, but the serotonin receptors--type 3 [5-(hydroxytryptamine) HT₃]-and the substance P receptors (NK₁ receptors) are most important.
- Dopamine D₂ receptors are of lesser importance but provided the key to current understanding of 5-HT₃ receptor.
- Other neurotransmitters(H1, M, GABA, CB) may have some effect on nausea, with a lesser effect on vomiting.

Pathophysiology of Emesis

- Fear, Dread, Anticipation → Higher level of cortex → 5HT₃, NK₁, D₂, GABA → Emetic Center In Medulla → Vomiting
- Inner Ear, Motion → Cerebellum → H₁, M → Emetic Center In Medulla (NK₁) → Vomiting
- Blood Born Emetics → Chemoreceptor Trigger Zone (CTZ) → 5HT, D₂, M, CB, Opioid → Emetic Center In Medulla (NK₁) → Vomiting
- Vagal, sympathetic stimulations → 5HT₃, NK₁, D₂, M, CB, H₁ → Emetic Center In Medulla (NK₁) → Vomiting

Anti-emetics Drug Classes- based on targeting receptor

- Histamine (H1)
 - Diphenhydramine (++++)
 - Promethazine (++++)
 - Prochlorperazine (++)
- Dopamine (D2)
 - Haloperidol (++++)
 - Metoclopramide (+++)
 - Olanzapine (++++)
 - Prochlorperazine(++++)
 - Promethazine (++)

Anti-emetics Drug Classes- based on targeting receptor

- Muscarinic acetylcholine receptors (M)
 - Scopolamine(++++)
 - Diphenhydramine(++)
 - Promethazine (++)
- Cannabinoid (CB)
 - Dronabinol
 - Nabilone
- GABA
 - Lorazepam

Corticosteroids: Dexamethasone

- Cornerstone of Antiemetic therapy(both Acute & Delayed N/V)
- MOA not well understood, possibly prostaglandin blocking activity in the cerebral cortex and changes in cellular permeability.
- Not recommended as single agent for high/moderate CINV
- Not recommended with immunotherapies and cellular therapies.
- SE: insomnia, agitation, increased energy, increased appetite, agitation, mood changes, Hyperglycemia w/prolonged use, dyspepsia & abdominal discomfort.
- Clinical pearl: consider extending the course for patients suffering from extended delayed CINV
- NK1 receptor antagonists(with the exception of Rolapitant) inhibit metabolism of Dexamethasone, reduce dose of dexamethasone.

Serotonin Receptor Antagonists

- The revolution in control of CINV happened when recognized the role of 5-HT₃ receptor subtype.
- Development of selective 5-HT₃ antagonist led to significant success in control of CINV.
- The 5-HT₃ receptors are located both centrally (NTS and AP) and in the periphery (GI) vomiting reflex arc.
- Oral and intravenous serotonin receptor antagonists (5-HT₃ RA) have equivalent efficacy when used at the appropriate doses and intervals.
- Clinical pearl: After receiving palonosetron, granisetron transdermal patch, or extended-release injection, breakthrough 5-HT₃ RAs play a limited role in the delayed infusion period and breakthrough antiemetic should focus on a different mechanism of action.

5 HT3 Receptor Antagonists

- Dolasetron 100 mg PO once.
- Granisetron 10 mg SQ once or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy.
- Ondansetron 16–24 mg PO once, or 8-16 mg IV once
- Palonosetron 0.25 mg IV once

Neurokinin-1 (NK1) receptor antagonists

Place in therapy is for prevention and not treatment of CINV. Largest benefit seen in delayed CINV setting.

- Aprepitant- 125 mg PO D1, then 80 mg D2&3; Aprepitant injectable emulsion 130 mg IV once.
Fosaprepitant- 150 mg IV once.
- Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once .
- Rolapitant- 180 mg PO once (has an extended half-life and should not be administered at less than 2-week intervals)

D2- DOPAMINE TYPE 2 RECEPTOR ANTAGONIST(METOCLOPRAMIDE)

- It was the 1st group of antiemetic that was used for the prevention of CINV.
- Initial Antiemetic therapy were focused on dopamine D2 receptors and dopaminergic antagonist such as metoclopramide
- Three proposed MOA contributing to its antiemetic properties:
 - Blocks dopamine at the chemoreceptor trigger zone (CTZ)
 - Stimulates cholinergic activity in the gut, causing increased gut motility
 - Blocks peripheral serotonin receptors in the GI & CTZ (high- dose only)
- Metoclopramide had limited efficacy in controlling CINV even when used in high dose and was significantly associated with side effect mainly extrapyramidal symptoms.

Olanzapine- Atypical antipsychotic

- Olanzapine 5-10 mg PO once daily X 4 days.
- SE: sedation, EPS, QTc prolongation
- CNS depression/sedation most notable on day 2 & improves over time
- Consider 5 mg dose for elderly or over-sedated patients
- May increase the risk of developing QTc prolongation, when used in combination with other QT-prolonging agents.

NEPA-Netupitant +Palonosetron

- Netupitant has half-life of 80 hours (vs. aprepitant half-life 9-13 hours)
- Inhibits CYP 3A4 up to 4 days following dose
- Phase 3 studies in highly- and moderately- emetogenic chemotherapy regimens demonstrated improved control of CINV in acute, delayed and overall phases
- Use with caution in patients receiving concomitant medications primarily metabolized by CYP3A4. The plasma concentrations of CYP3A4 substrates can increase when co-administered. The inhibitory effect on CYP3A4 can last for multiple days.
 - A two-fold increase in the systemic exposure of dexamethasone was observed 4 days after single dose of Netupitant, reduced dose of Dexamethasone should be given.
 - Consider the potential effects of increased plasma concentrations of midazolam or other benzodiazepines metabolized via CYP3A4 (alprazolam, triazolam). when administering with Netupitant, the systemic exposure to midazolam was significantly increased
- Avoid concomitant use with a strong CYP3A4 inducer such as rifampin.

PRINCIPLES OF EMESIS CONTROL in CANCER PATIENT

Prevention of nausea/vomiting is the goal

- Evaluate the risk for nausea/vomiting.
- Consider other potential causes of emesis: brain metastasis, gastroparesis, etc.
- Review concomitant drugs including opioids
- Multidrug regimen vs single drug regimen
- Acute ≤ 24 hours vs. delayed nausea > 24 hours.
- High emetogenic potential chemotherapy vs. moderate emetic risk.
- Be aware of the potential for the overuse of prophylactic antiemetics
- Unwanted potential Adverse effects & pose undue economic burden

NCCN Guideline For Anti-emesis Recommendation- Single Day Highly Emetogenic Regimens, Acute

- NK1-RA + 5HT3-RA +Dexamethasone

OR

Palonosetron 0.25 mg IV + Olanzapine 10 mg PO + Dexamethasone 12

OR

Olanzapine + NK1-RA+ 5H3-RA + Dexamethasone

NCCN Guidelines for Antiemesis: Recommendations for Delayed, Highly Emetogenic of single day regimen

Used D1 for Acute N/V	Use for Delayed N/V
Aprepitant 125+5HT3 +Dex 12	Aprepitant 80 Days 2-3+ Dexamethasone 8 Days 2-4
Olanzapine 10 PO + Dex 12 PO/IV + Palonosetron 0.25 IV	Olanzapine 10 mg PO daily on days 2, 3, 4
Olanzapine 10 + 5HT3 + NK1+ Dex	Olanzapine 10 mg PO daily on days 2, 3, 4. Aprepitant 80 mg PO daily on days 2, 3 (if Aprepitant PO used on day 1) Dexamethasone 8 mg PO/IV daily on days 2, 3, 4

NCCN Guidelines for Antiemesis : Recommendations for Acute & Delayed, Moderately Emetogenic

Used for Acute N/V Day 1	Use for Delayed N/V Days 2-3
5HT3 + Dex (Palonosetron 0.25 mg IV once preferred)	<ul style="list-style-type: none"> Dex 8mg PO/IV Days 2&3 Nothing if Palonosetron was used in acute setting
NK1-RA + 5HT3 + Dexamethasone	Aprepitant 80 D2-3 +/- Dexamethasone D2,D3
Olanzapine + Palonosetron + Dex	Olanzapine 10 mg PO daily on days 2, 3

NCCN Guidelines for Antiemesis: Recommendations for prevention of emesis with LOW AND MINIMAL emetic risk agents

Low Emetic Risk- Start before chemotherapy, Repeat daily for multiday doses of chemotherapy.

Select one:

- Dexamethasone 8–12 mg PO/IV once
- Metoclopramide 10–20 mg PO/IV once
- 5-HT3 RA

Minimal Emetogenic Risk:

- No Routine Prophylaxis

ORAL CHEMOTHERAPY - EMESIS PREVENTION

High to moderate emetic risk:

- Select one of the 5-HT3 RA
- Start before chemotherapy and continue daily .

Low to minimal emetic risk:

Prn Recommendation only, unless N/V occurs, then select any agent & continue daily

Multiday Regimens

- Multiday chemotherapy regimens are common and introduce a challenge in the management of CINV because of the overlap between acute and delayed CINV.
- After chemotherapy administration concludes, the period of risk for delayed emesis also depends on the specific regimen and the emetogenic potential of the last chemotherapy agent administered in the regimen.
- Practical issues: take into account the administration setting (eg, inpatient versus outpatient), preferred route of administration (parenteral, oral, or transdermal), duration of action of the 5-HT3 RA and appropriate associated dosing intervals, tolerability of daily antiemetics (eg, steroids), adherence/compliance issues, and individual risk factor(s).
- Dexamethasone dose may be modified or omitted when the chemotherapy regimen already includes a steroid
- If patients cannot tolerate dexamethasone, consider replacing with olanzapine.

Breakthrough CINV- Occurs despite Proper prophylaxis, Measures by means of “prn” medications

The general principle of breakthrough treatment is to add one agent from a different drug class to the current regimen

- Add anxiolytic
- Add H2-blocker/PPI
- Add Aprepitant
- Add olanzapine
- Add dopamine antagonist
- Change dose/schedule of serotonin antagonist
- If palliative, change chemotherapy
- If controlled N/V, then continue breakthrough medications, on a schedule & PRN
- If N/V not controlled: Re-evaluate and consider dose adjustments and/ or sequentially add one agent from a different drug class

Audience Response Question #3

JD is a 40-year old depressed woman who was recently diagnosed with extensive stage small cell lung cancer. She is a social drinker, stopped smoking 15 years ago. Her PMH is significant for morning sickness with her 2 pregnancies and motion sickness. Her oncologist wishes to use cisplatin 75 mg/m² IV D1, etoposide 100 mg/m² IV D1-3 of every 28 days for 6 cycles.

What should she receive for prevention of acute CINV?

- A- Fosaprepitant 150 mg IV plus palonosetron 0.25 mg IV plus dexamethasone 20 mg PO
- B- Fosaprepitant 150 mg IV plus palonosetron 0.25 mg IV plus dexamethasone 12 mg PO
- C- Fosaprepitant 150 mg IV plus ondansetron 8 mg PO plus dexamethasone 20 mg PO
- D- Fosaprepitant 150 mg IV plus ondansetron 8 mg PO plus dexamethasone 12 mg PO

Answer to Audience Question#3

Correct answer is B

- Current NCCN Guidelines: 3 drugs (NK1 antagonist, 5HT3 agonist & dexamethasone) for the prevention of acute emesis due to highly emetogenic chemotherapy.
- Fosaprepitant 150 mg IV is single dose on D1.
- Due to an interaction between Aprepitant / Fosaprepitant and dexamethasone, it is recommended that the dose of dexamethasone be decreased from 20 mg to 12 mg prior to chemotherapy.
- The correct dose for PO ondansetron is 16 to 24 mg.

Note: Olanzapine regimens may also be used for highly emetic chemotherapy (it was not listed as one of the choices)

Audience Response Question#4

Based on your answer for antiemetic regimen for acute N/V on D1, what should JD receive for prevention of delayed nausea and vomiting?

- A- Dexamethasone 8 mg PO QD on days 2 to 4
- B- Dexamethasone 8 mg PO QD days 2 to 4 plus ondansetron 8 mg PO days 2 to 4
- C- Aprepitant 80 mg PO on days 2 and 3 plus dexamethasone 8 mg PO QD on days 2 to 4
- D- Aprepitant 80 mg PO on days 2 and 3 plus dexamethasone 8 mg PO QD days 2 to 4 plus ondansetron 8mgPOdays2 to 4

Answer to Audience Response Question #4

- Correct answer is A.
- Since JD received fosaprepitant 150 mg on day 1, no additional Aprepitant is necessary for this cycle. Therefore, single dexamethasone 8 mg PO QD on days 2 to 4 is the correct answer.
- 5HT₃ not recommended in general for prevention of delayed nausea and vomiting due to highly emetogenic chemotherapies

Conclusion

- CINV can significantly affect patient's quality of life, compliance, and provider's ability to administer further chemotherapy treatment.
- Appropriate use of antiemetics & adherence to evidence based consensus guidelines decreases incidence of CINV.
- The advent of 5-HT₃ and NK₁ antagonists that specifically target neuroreceptors implicated in CINV has dramatically improved the prevention and acute control of symptoms.
- However, delayed CINV remains difficult to control and poses a substantial burden for patients.
- Proper assessment of CINV risk and its management allow pharmacists the opportunities to become more directly involved in the care of cancer patients receiving chemotherapy
- Pharmacists & Pharmacy technicians can ensure that patients are given appropriate prescriptions and can facilitate patients obtaining the medications.

Questions?



References

- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis V.3.2018 © National Comprehensive Cancer Network, Inc 2018. All rights reserved. Accessed September, 2018.
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