

Management and Treatment of Cancer Patients with Chemotherapy Induced Nausea and Vomiting

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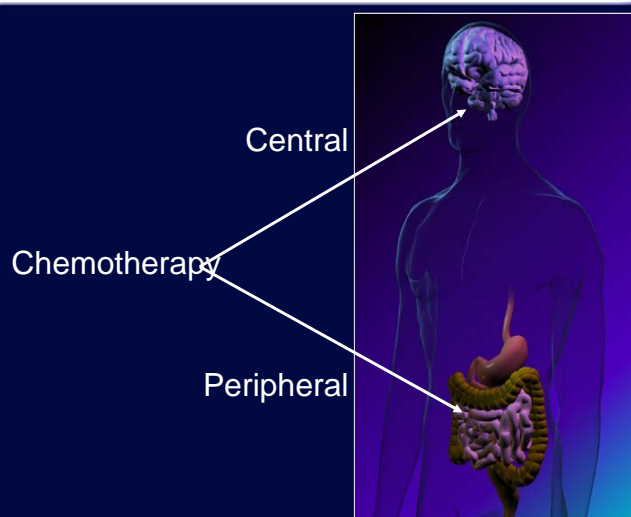
Comprehensive Cancer Center

Outline

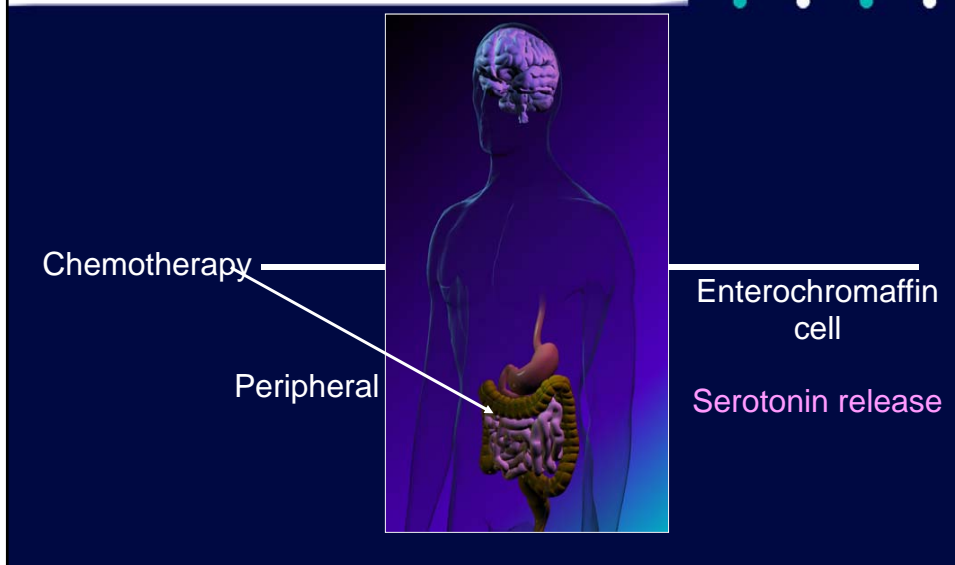
- Mechanisms of Chemotherapy Induced Nausea and Vomiting (CINV)
- Risk Factors
- Emetogenicity of Chemotherapy Agents
- Treatment

Mechanisms of CINV

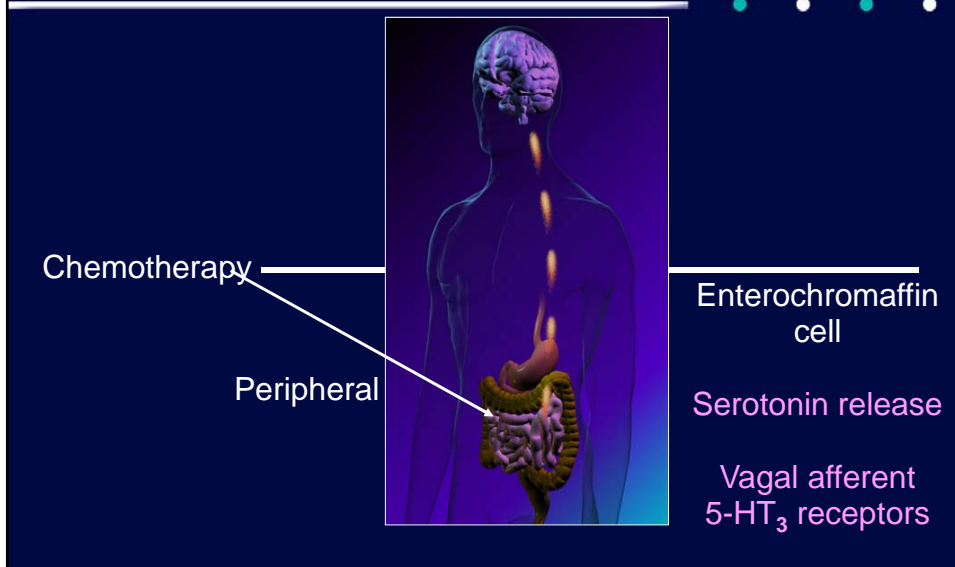
Mechanisms of Chemotherapy-Induced Nausea and Vomiting



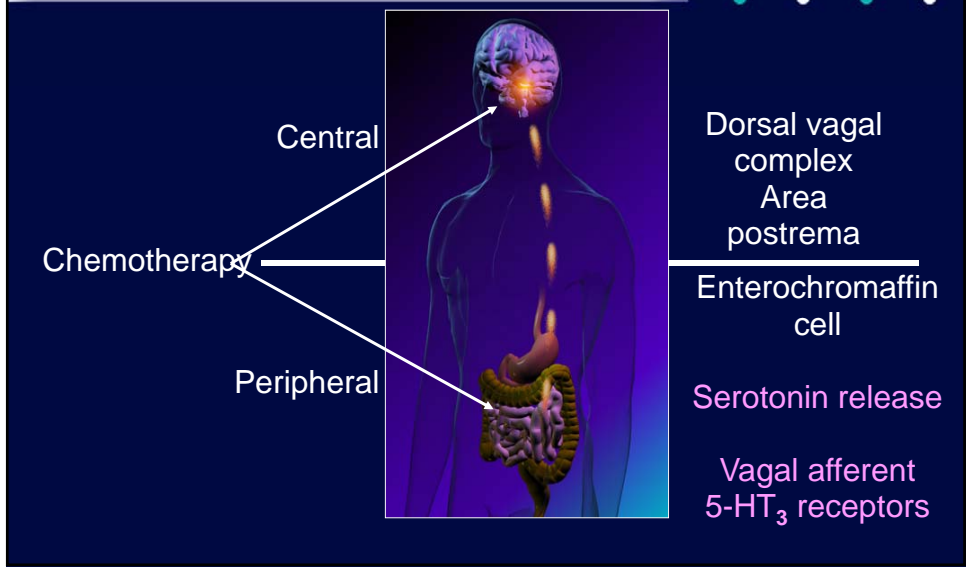
Mechanisms of Chemotherapy-Induced Nausea and Vomiting



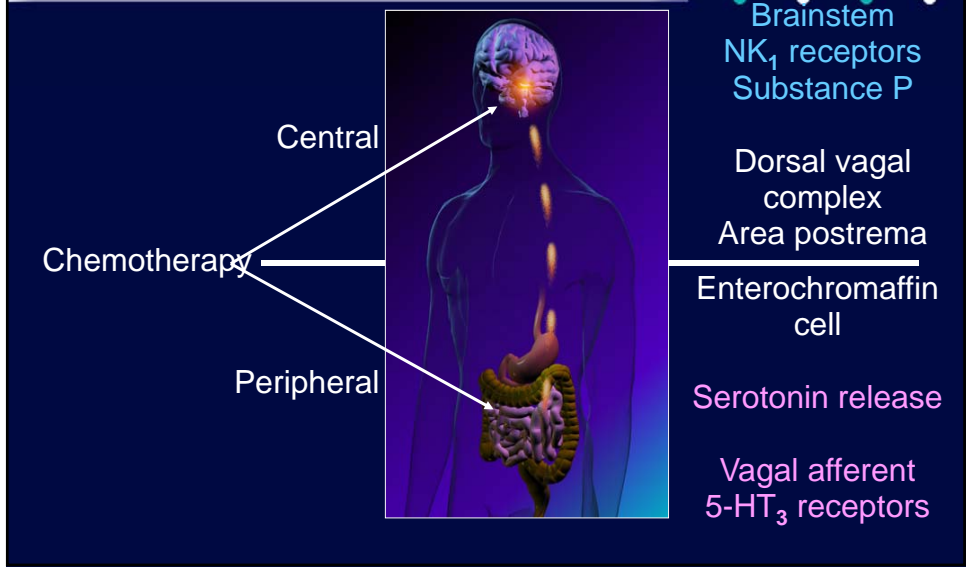
Mechanisms of Chemotherapy-Induced Nausea and Vomiting

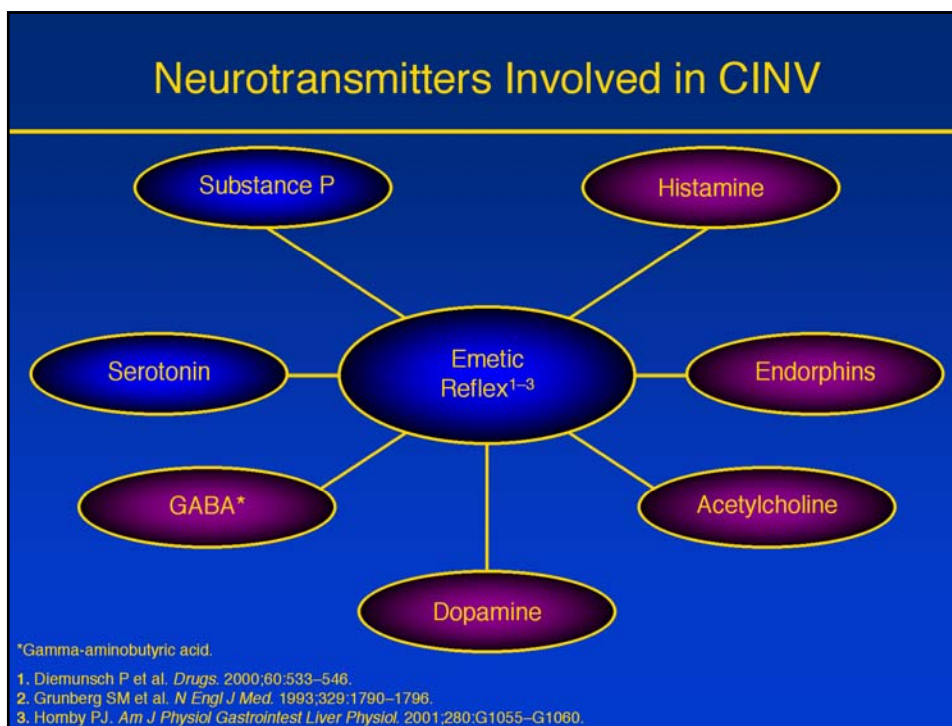


Mechanisms of Chemotherapy-Induced Nausea and Vomiting



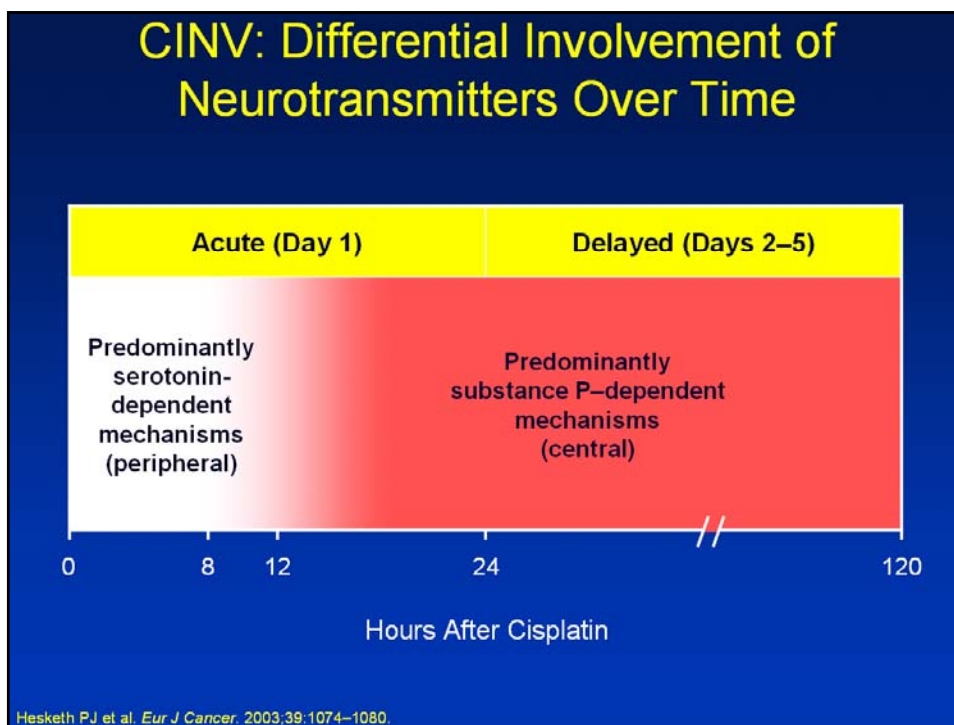
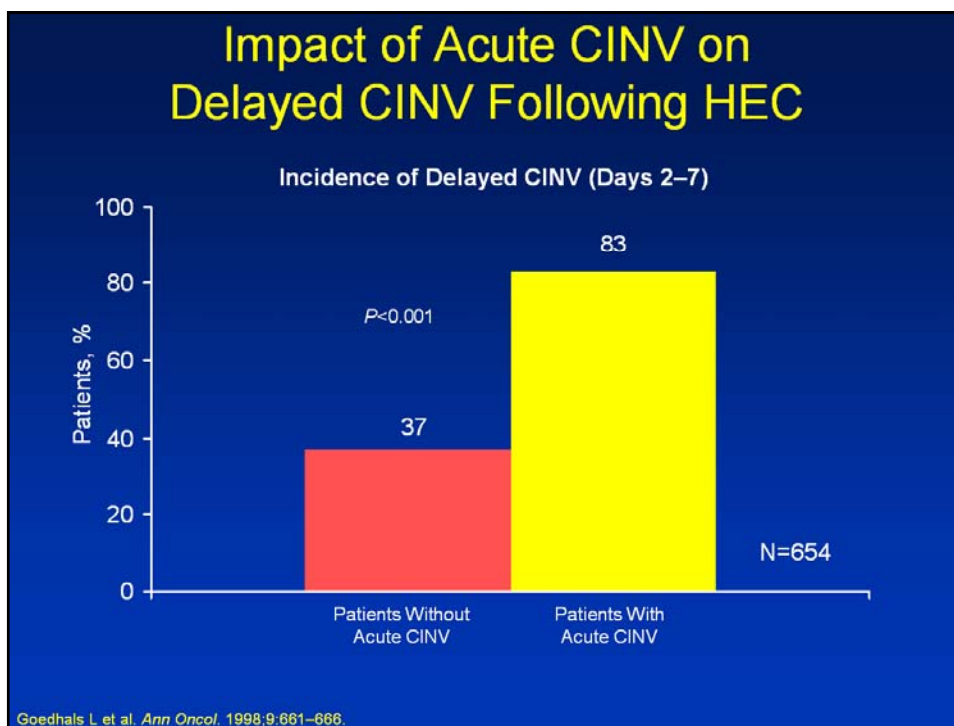
Mechanisms of Chemotherapy-Induced Nausea and Vomiting





Acute Vs. Delayed CINV

- **Acute CINV**
 - Nausea and vomiting that occurs within the first 24 hours after administration of chemotherapy
 - Most emesis occurs within 1-3 hours after administration
- **Delayed CINV**
 - Nausea and vomiting starting more than 24 hours after administration of chemotherapy



Types of Emesis

- **Anticipatory CINV**
 - Conditioned response, happens after a negative past experience with chemotherapy
 - 18-57%
- **Breakthrough CINV**
 - Occurs despite prophylaxis, and requires rescue

Risk Factors for CINV

Risk Factors

- Which of the following is a risk factor for CINV?
 - A. Male gender
 - B. Heavy alcohol consumption
 - C. Age < 50
 - D. Smoker

Risk Factors

- Which of the following is a risk factor for CINV?
 - A. Male gender
 - B. Heavy alcohol consumption
 - **C. Age < 50**
 - D. Smoker

Risk Factors Related to the Patient

- Low alcohol consumption (< 10 drinks/week)
- Younger age (< 50 y.o.)
- Female gender
- History of motion sickness
- Poor control with prior chemotherapy

Classification of Acute Emetogenic Potential of Single Chemotherapeutic Agents

Level 5	Emesis in >90% of patients
Level 4	Emesis in 60%–90% of patients
Level 3	Emesis in 30%–60% of patients
Level 2	Emesis in 10%–30% of patients
Level 1	Emesis in <10% of patients

Adapted from Hesketh PJ et al. *J Clin Oncol*. 1997;15:103–109, ©1997, with permission from the American Society of Clinical Oncology.

Single Chemotherapeutic Agents With Highest Potential for Acute Emesis

Level	Frequency of Emesis	Agent
5	>90%	Carmustine >250 mg/m ² Cisplatin ≥50 mg/m ² Cyclophosphamide >1,500 mg/m ² Dacarbazine Mechlorethamine Streptozocin
4	60%–90%	Carboplatin Carmustine ≤250 mg/m ² Cisplatin <50 mg/m ² Cyclophosphamide >750 mg/m ² ≤1,500 mg/m ² Cytarabine >1 g/m ² Doxorubicin >60 mg/m ² Methotrexate >1,000 mg/m ² Procarbazine (oral)

Adapted from Hesketh PJ et al. *J Clin Oncol.* 1997;15:103–109, ©1997, with permission from the American Society of Clinical Oncology.

Single Chemotherapeutic Agents With Moderate Potential for Acute Emesis

Level	Frequency of Emesis	Agent
3	30%–60%	Cyclophosphamide ≤750 mg/m ² Cyclophosphamide (oral) Doxorubicin 20–60 mg/m ² Epirubicin ≤90 mg/m ² Hexamethylmelamine (oral) Idarubicin Ifosfamide Irinotecan Methotrexate 250–1,000 mg/m ² Mitoxantrone <15 mg/m ²
2	10%–30%	Capecitabine Docetaxel Etoposide 5-Fluorouracil <1,000 mg/m ² Gemcitabine Methotrexate >50 mg/m ² <250 mg/m ² Mitomycin Paclitaxel Topotecan

Adapted from Hesketh PJ et al. *J Clin Oncol.* 1997;15:103–109, ©1997, with permission from the American Society of Clinical Oncology.

Single Chemotherapeutic Agents With Lowest Potential for Acute Emesis

Level	Frequency of Emesis	Agent
1	<10%	Bleomycin Busulfan Chlorambucil (oral) 2-Chlorodeoxyadenosine Fludarabine Hydroxyurea Methotrexate ≤ 50 mg/m ² L-phenylalanine mustard (oral) Thioguanine (oral) Vinblastine Vincristine Vinorelbine

Adapted from Hesketh PJ et al. *J Clin Oncol*. 1997;15:103-109, ©1997, with permission from the American Society of Clinical Oncology.

Emetogenicity of Commonly Used Combination Regimens

Cancer Type	Commonly Used Combination	Average Dose (mg/m ² /Day)	Hesketh Level
Breast	AC	Cyclophosphamide 579.46 Doxorubicin 58.05	4
	CMF	Cyclophosphamide 506.56 Methotrexate 41.13 Fluorouracil 564.59	4
Non-Small-Cell Lung	Carboplatin/Paclitaxel	Carboplatin 239.55 Paclitaxel 121.85	5
	Cisplatin/Etoposide	Cisplatin 48.23 Etoposide 76.01	5

Tandem Anticancer Drug and Tumor Audit; November 2002–October 2003.

Emetogenicity of Commonly Used Combination Regimens (cont)

Cancer Type	Commonly Used Combination	Average Dose (mg/m ² /Day)	Hesketh Level
Colorectal	5FU/ Leucovorin/Oxaliplatin	Fluorouracil 776.69 Leucovorin 232.05 Oxaliplatin 82.77	4
	5FU/ Irinotecan/Leucovorin	Fluorouracil 537.68 Irinotecan 105.46 Leucovorin 69.35	4
	5FU/ Leucovorin	Fluorouracil 456.06 Leucovorin 298.17	2
Ovarian	Carboplatin/ Paclitaxel	Carboplatin 321.75 Paclitaxel 165.02	5
	Carboplatin/ Docetaxel	Carboplatin 266.74 Docetaxel 58.79	5

Tandem Anticancer Drug and Tumor Audit; November 2002–October 2003.

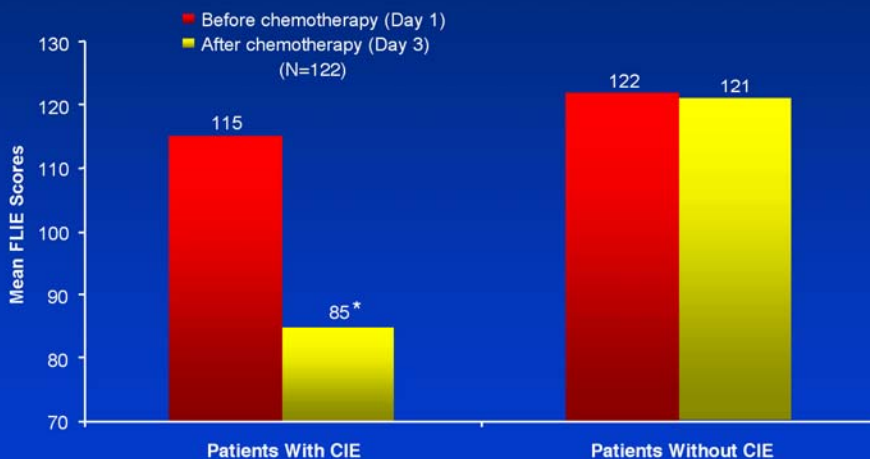
Side Effects Most Distressing to Patients Undergoing Emetogenic Chemotherapy

Identical Surveys Conducted Before and After the Availability of 5-HT₃ Antagonists Show Little Change in Patient Perceptions

1983		1995	
Rank	Symptoms	Rank	Symptoms
1	Vomiting	1	Nausea
2	Nausea	2	Loss of hair
3	Loss of hair	3	Vomiting

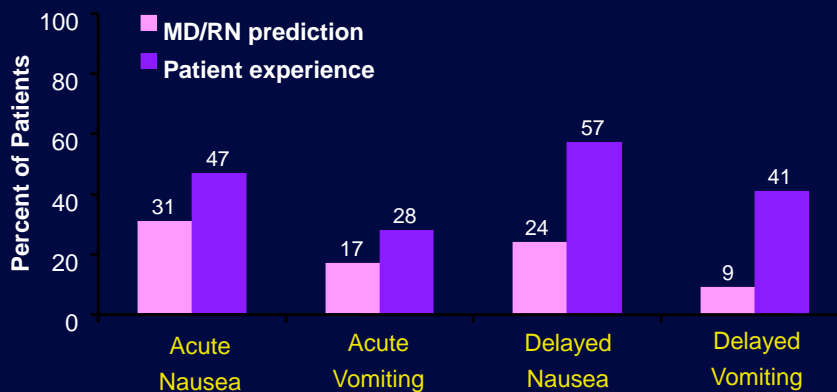
Adapted from de Boer-Dennert et al. *Br J Cancer*. 1997;76:1055–1061, ©1997, with permission from Nature Publishing Group.

Impact of CINV on Health-Related Quality of Life: Functional Living Index–Emesis (FLIE)



*P=0.001
Adapted from Lindley CM et al. *Qual Life Res.* 1992;1:331–340, ©1992 with kind permission from Kluwer Academic Publishers.

Perceptions and Reality: Moderately Emetogenic Chemotherapy



MD/RN: Physicians and nurses from 6 oncology practices.
Patients: 75% women; 90% received agents with moderate emetogenic risk.

Grunberg SM et al. *Proc Am Soc Clin Oncol.* 2002;21(Part 2):250a. Abstract #996.

Treatment of CINV and Guidelines

NCCN Guidelines

- Strives to be comprehensive
- Tries to provides advice for most clinical situations; reviewed annually
- Category 1 recommendations: high level of evidence-based data
- Category 2B: best available evidence
 - Not always supported by high-level clinical trials
 - Consensus among experts is not complete
 - Combination of clinical trial evidence and expert opinion

Case

- A 45 year old patient with ovarian cancer will be treated with carboplatin and paclitaxel. What antiemetic regimen would you prescribe on the day of treatment?
 - A. Ondansetron and aprepitant
 - B. Palinosetron and dexamethasone
 - C. Granisetron, prochlorperazine, and lorazepam
 - D. Ondansetron, aprepitant, and dexamethasone

Case

- A 45 year old patient with ovarian cancer will be treated with carboplatin and paclitaxel. What antiemetic regimen would you prescribe on the day of treatment?
 - A. Ondansetron and aprepitant
 - B. Palinosetron and dexamethasone
 - C. Granisetron, prochlorperazine, and lorazepam
 - D. **Ondansetron, aprepitant, and dexamethasone**

Therapy for Highly Emetogenic Chemotherapy

Highly Emetogenic Chemotherapy

- Serotonin Antagonist
- Dexamethasone
- NK1 Antagonist

NCCN Antiemesis Clinical Practice Guidelines: Highly Emetogenic Chemotherapy

Start before chemotherapy:

- **Aprepitant** 125 mg po or Fosaprepitant 115 IV day 1, 80 mg p.o. days 2-3
- and*
- **Dexamethasone** 12 mg po or IV, days 1-4
- and*
- **5-HT₃ antagonist:**
 - Palonosetron 0.25 mg IV day 1 (preferred, Category 2B)
 - or*
 - Dolasetron 100 mg po or 1.8 mg/kg IV or 100 mg IV day 1
 - or*
 - Granisetron 2 mg po or 1 mg po bid, or 0.01 mg/kg IV day 1 or transdermal patch containing 34.3 mg granisetron applied 24 hours before chemo, maximum duration of patch is 5 days
 - or*
 - Ondansetron 16-24 mg po or 8-12 mg IV day 1
- and*
- +/- Lorazepam 0.5-2 mg po, IV, or s.l. q 4-6 hrs prn days 1-4
- +/- H2 blocker or proton pump inhibitor

Serotonin Antagonists

Double-blind comparative studies of 5-HT₃ antagonists for acute emesis following cisplatin chemotherapy

Author, year	Cisplatin dose	Regimens	Complete response (%)
Navari, 1995	≥ 60 mg/m ²	O 0.15 mg/kg x 3 i.v.	51
		G 10 mcg/kg i.v.	47
		G 40 mcg/kg i.v.	48
Gralla, 1998	≥ 60 mg/m ²	O 32 mg i.v.	58
		G 2 mg p.o.	55
Ruff, 1984	≥ 50 mg/m ²	O 8 mg i.v.	59
		O 32 mg i.v.	51
		G 3 mg i.v.	56
Italian Group, 1995	≥ 50 mg/m ²	O 8 mg i.v.	78
		G 3 mg i.v.	80
Audhuy, 1996	≥ 80 mg/m ²	D 1.8 mg/kg i.v.	54
		D 2.4 mg/kg i.v.	47
		G 3 mg iv	48
Hesketh, 1996	≥ 70 mg/m ²	D 1.8 mg/kg i.v.	44
		D 2.4 mg/kg i.v.	40
		O 32 mg iv	43
Marty, 1995	≥ 50 mg/m ²	O 32 mg i.v.	85
		T 5 mg i.v.	54

O = Ondansetron G = Granisetron
D = Dolasetron T = Tropisetron

Hesketh, Cancer Invest 2000; 18: 163

Palonosetron (Aloxi™)

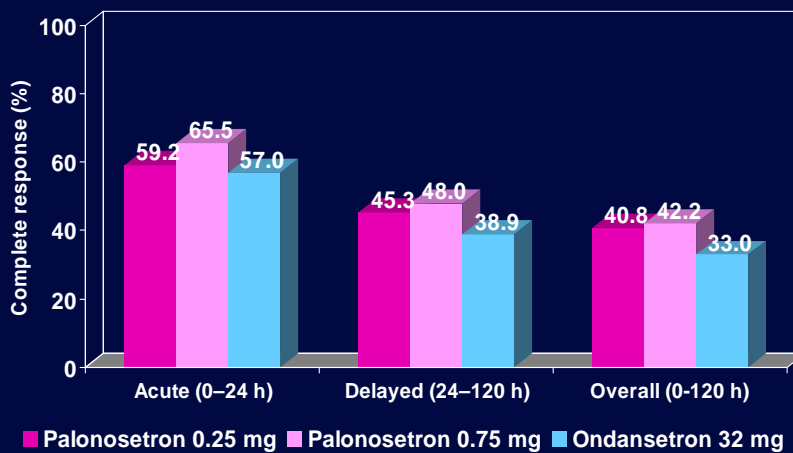
- A 5-HT₃ receptor antagonist synthesized to have a prolonged duration of action
- Beneficial features
 - Long half-life: ~40 hours vs 4–8 hours
 - Greater receptor binding affinity: 100-fold higher

Palonosetron vs Ondansetron in Patients Receiving **Highly** Emetic Chemotherapy

- Randomized, multicenter, double-blind, stratified, parallel-arm trial
- Active comparator trial
 - Palonosetron 0.25 mg IV
 - Palonosetron 0.75 mg IV
 - Ondansetron 32 mg IV
- Dexamethasone used on day 1 prior to chemotherapy at investigator's discretion

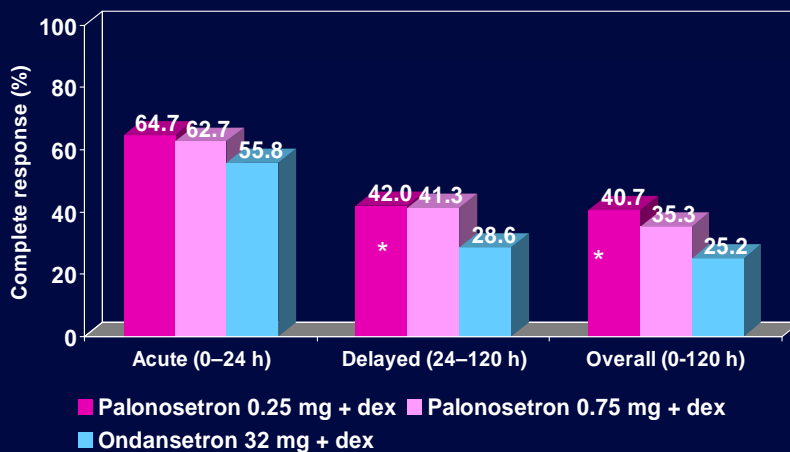
Aapro M, et al. *Support Care Cancer*. 2003;11:391.

Palonosetron vs Ondansetron in Highly Emetic Chemotherapy



Aapro M, et al. *Support Care Cancer*. 2003;11:391.

Subset Analysis of Patients Receiving Dexamethasone (N = 447)



*97.5% CI for differences between palonosetron 0.25 mg and ondansetron 32 mg indicates palonosetron superiority

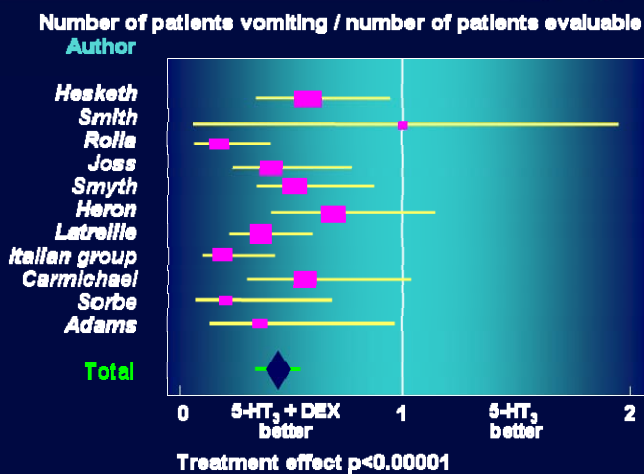
Aapro M, et al. *Support Care Cancer*. 2003;11:391.

Indications and Usage

- ALOXI (palonosetron) is indicated for:
 - the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic chemotherapy
 - the prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy.
 - The first 5-HT₃ receptor antagonist specifically indicated for delayed CINV

Add a Steroid

The effect of adding dexamethasone to 5-HT₃ antagonists on acute emesis



Jantunen et al, Eur J Cancer 1997; 33: 66

Dose response of dexamethasone: Randomized trial

Dexamethasone dose level	Complete control: Vomiting	Complete control: Nausea
4 mg i.v. day 1 (n = 133)	69%	61%
8 mg i.v. day 1 (n = 136)	69%	61%
12 mg i.v. day 1 (n = 130)	79%	67%
20 mg i.v. day 1 (n = 131)	83%*	71%

* p<0.009, 20 mg vs 4 mg and 8 mg levels

Italian Group, J Clin Oncol 1998; 16: 2937

Delayed Nausea and Vomiting

- Recent meta-analysis of randomized controlled trials
 - Adding a serotonin antagonist to dexamethasone did not improve the antiemetic effect of dexamethasone for preventing delayed emesis

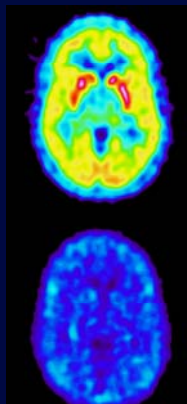
NK1 Antagonist

Aprepitant: Mechanism of Action

- Selective high affinity antagonist of neurokinin1 (NK1) receptors (natural substrate is Substance P)
- Little or no affinity for serotonin, dopamine, and corticosteroid receptors
- Animal and human PET scan studies show that it crosses the blood brain barrier and occupies brain NK1 receptors

Aprepitant Blocks Brain NK₁ Receptors in Humans

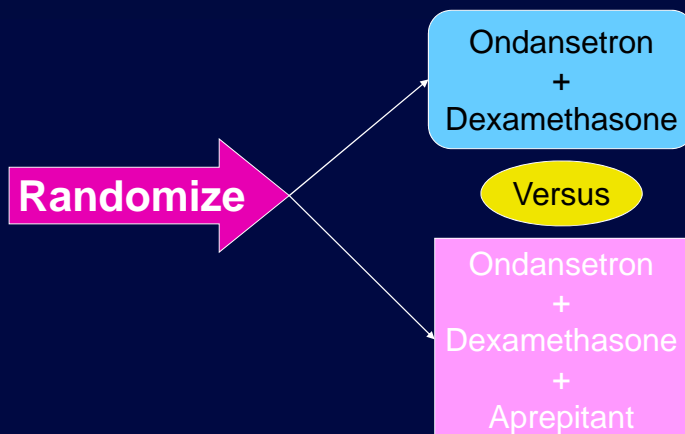
Binding of PET tracer to NK₁ receptors prior to aprepitant dosing



Blockade of NK₁ receptors after aprepitant dosing



Aprepitant in Patients Receiving Cisplatin: Randomized Trials (052/054)



Warr D, et al. 39th ASCO Annual Meeting, 2003. Abstract #2919.

Aprepitant (Emend®) Randomized Trials (052/054): Treatment Regimens (N = 1103)

Group	Day 1			Days 2-3		Day 4
	O	D	A	D	A	D
Aprepitant	32	12	125	8	80	8
Control	32	20	P	16	P	16

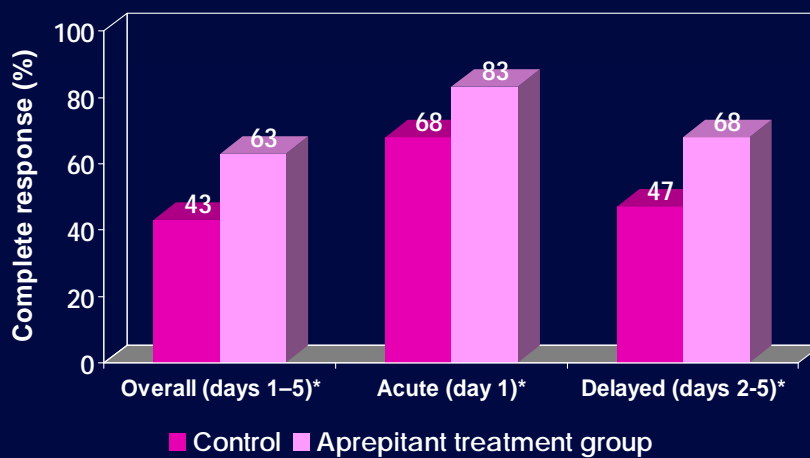
O = ondansetron, D = dexamethasone, A = aprepitant, P = placebo

Warr D, et al. 39th ASCO Annual Meeting, 2003. Abstract #2919.

Primary Endpoint: Complete Response

- Complete response
 - No emesis
 - No use of rescue medications for nausea or vomiting
- Primary endpoint: Overall complete response
 - Secondary endpoints: acute and delayed complete response

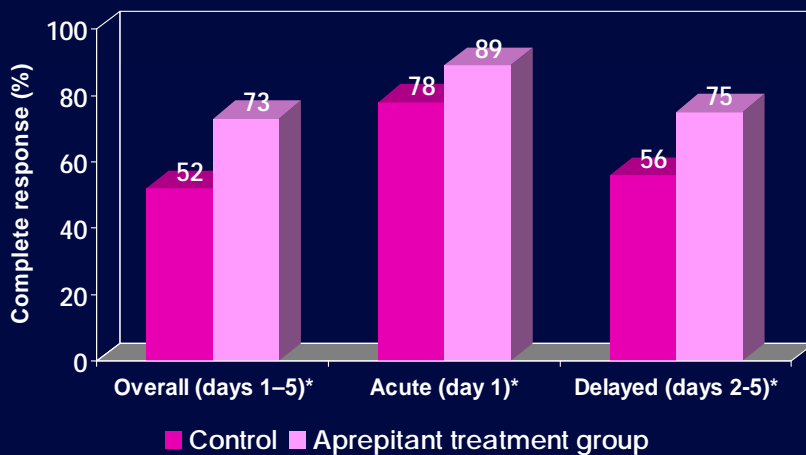
Aprepitant Phase III Trial 054: Complete Response (N = 523)



* $P < 0.001$

Warr D, et al. 39th ASCO Annual Meeting, 2003. Abstract #2919.

Aprepitant Phase III Trial 052: Complete Response (N = 520)



* $P < 0.001$

Warr D, et al. 39th ASCO Annual Meeting, 2003. Abstract #2919.

Aprepitant: Indications

- EMEND (aprepitant), in combination with other antiemetic agents, is indicated for prevention of:
 - Acute and delayed nausea and vomiting associated with initial and repeat courses of **highly** emetogenic cancer chemotherapy, including high-dose cisplatin
 - Nausea and vomiting associated with initial and repeat courses of **moderately** emetogenic cancer chemotherapy

Dosage and Administration

- EMEND® (aprepitant) is given for 3 days as part of a regimen that includes a corticosteroid and a 5-HT₃ antagonist.
- The recommended dose of EMEND is 125 mg orally 1 hour prior to chemotherapy treatment (Day 1) and 80 mg once daily in the morning on Days 2 and 3.
- EMEND has not been studied for the treatment of established nausea and vomiting.

Therapy for Moderately Emetogenic Chemotherapy

Moderately Emetogenic Chemotherapy

- Serotonin Antagonist
- Dexamethasone
- NK1 Antagonist

NCCN Antiemesis Clinical Practice Guidelines: Moderately Emetogenic Chemotherapy

Day 1 – Start before chemotherapy:

- Aprepitant 125 mg po or Fosaprepitant 115 mg I.V. in select pts

and

- Dexamethasone 12 mg po or IV

and

- 5-HT₃ antagonist:
Dolasetron *or*
Granisetron *or*
Ondansetron *or*
Palonosetron

and

- +/- Lorazepam
- +/- H2 blocker or proton pump inhibitor

Days 2 - 3:

- Aprepitant 80 mg po qd and +/- Dexamethasone 12 mg po/IV qd

or

- Dexamethasone 12 mg po/IV qd

or

- 5-HT₃ antagonist:
Dolasetron *or*
Granisetron *or*
Ondansetron

or

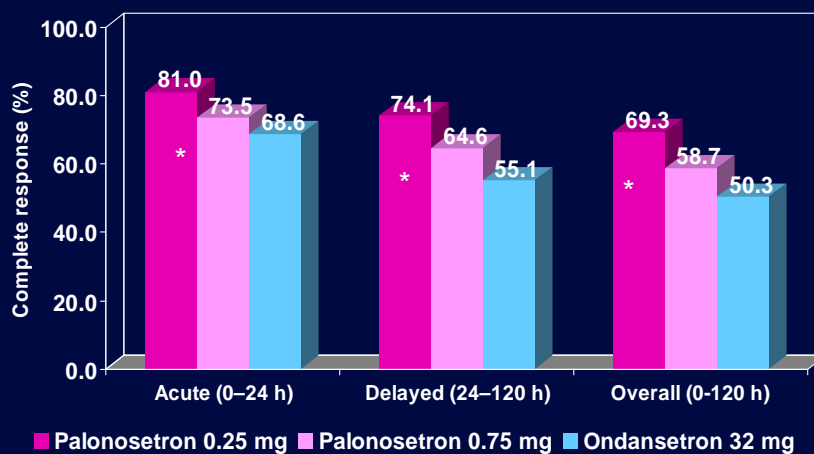
- +/- Lorazepam
- +/- H2 blocker or proton pump inhibitor

Palonosetron vs Ondansetron in Patients Receiving Moderately Emetic Chemotherapy

- Randomized, multicenter, double-blind, stratified, parallel-arm trial
- Active comparator trial
 - Palonosetron 0.25 mg IV
 - Palonosetron 0.75 mg IV
 - Ondansetron 32 mg IV
- No corticosteroid administered as a pretreatment

Aapro M, et al. *Proc Am Soc Clin Oncol*. 2003. Abstract 2918.

Palonosetron vs Ondansetron in Moderately Emetic Chemotherapy



* 97.5% CIs for the difference vs ondansetron indicates superiority ($P < 0.025$)

Aapro M, et al. *Proc Am Soc Clin Oncol*. 2003. Abstract 2918.

Aprepitant (Emend®) Randomized Trial Patients Receiving AC-based Chemotherapy

Group	Day 1			Days 2-3	
	O	D	A	O	A
Aprepitant	8 mg BID	12 mg	125 mg	P	80 mg
Standard	8 mg BID	20 mg	P	8 mg BID	P

O = ondansetron PO

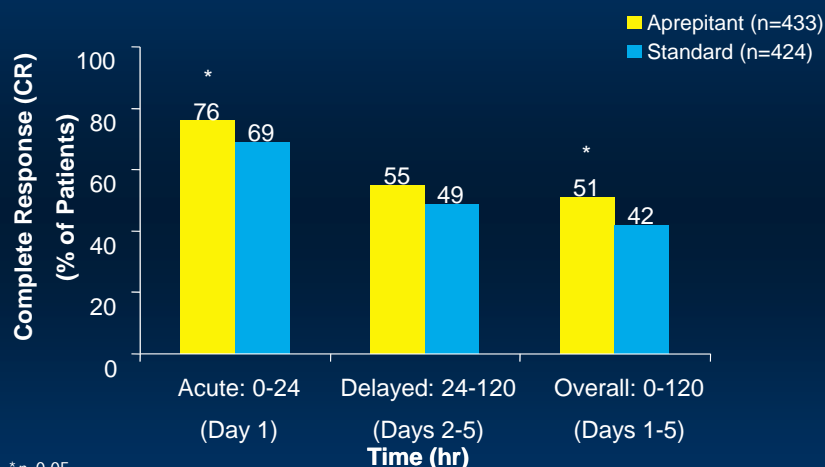
A = aprepitant PO

D = dexamethasone PO

P = placebo PO

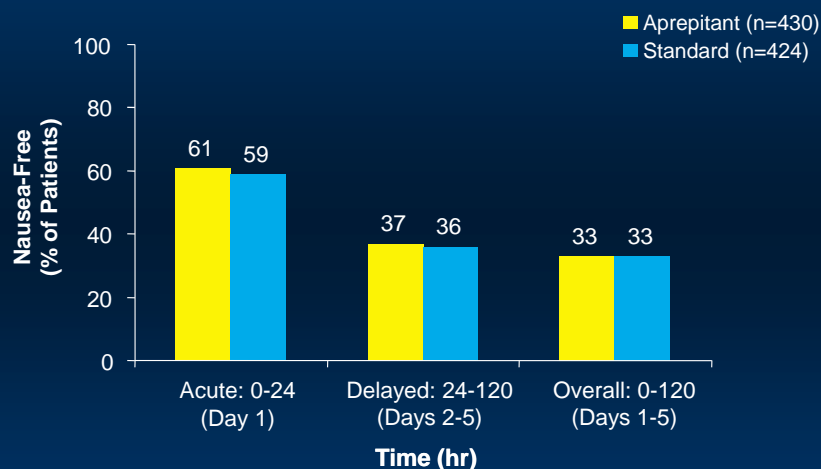
Warr DG et al. *J Clin Oncol* 2005; 23:2822-2830

Aprepitant in Moderately Emetogenic Chemotherapy: Complete Response (N=857)



Complete response (CR): no emesis and no rescue medication.
Warr DG et al. *J Clin Oncol* 2005; 23:2822-2830

Aprepitant in Moderately Emetogenic Chemotherapy: Percent of Patients with No Nausea



No nausea: score <5 mm on 0-100 mm VAS.
Warr DG et al. *J Clin Oncol* 2005; 23:2822-2830

New NK1 Antagonist: Casopitant

- Phase III trial
 - 1,917 evaluable pts
 - Moderately emetogenic chemotherapy - mostly AC-based regimen (adriamycin & cyclophosphamide)
 - 4 arms
 - All arms - ondansetron 8 mg p.o. b.i.d. days #1-3
 - All arms - dexamethasone 8 mg I.V. day #1
 - Placebo vs. single dose oral casopitant vs. 3 day oral casopitant vs. 3 day oral and I.V. casopitant

New NK1 Antagonist: Casopitant Results

- All 3 casopitant arms were the same: complete response was 73%, 73%, 74%.
- Control arm (placebo): 59% ($p < .0001$)
- Casopitant on days 2 and 3 did not seem to add efficacy
- Conclusion: Single dose of NK1 antagonist provides superior prevention of CINV in MEC, given with standard 2-drug antiemetic regimen

Case

- A 60 year old patient with esophageal cancer is going to receive single agent paclitaxel as palliative therapy for his metastatic disease. What antiemetic regimen would you prescribe?
- Ondansetron and dexamethasone
- Prochlorperazine
- Palonosetron, aprepitant, and dexamethasone
- Granisetron

Single Chemotherapeutic Agents With Moderate Potential for Acute Emesis

Level	Frequency of Emesis	Agent
3	30%–60%	Cyclophosphamide ≤ 750 mg/m ² Cyclophosphamide (oral) Doxorubicin 20–60 mg/m ² Epirubicin ≤ 90 mg/m ² Hexamethylmelamine (oral) Idarubicin Ifosfamide Irinotecan Methotrexate 250–1,000 mg/m ² Mitoxantrone <15 mg/m ²
2	10%–30%	Capecitabine Docetaxel Etoposide 5-Fluorouracil $<1,000$ mg/m ² Gemcitabine Methotrexate >50 mg/m ² <250 mg/m ² Mitomycin Paclitaxel Topotecan

Adapted from Hesketh PJ et al. *J Clin Oncol*. 1997;15:103–109, ©1997, with permission from the American Society of Clinical Oncology.

Case

- A 60 year old patient with esophageal cancer is going to receive single agent paclitaxel as palliative therapy for his metastatic disease. What antiemetic regimen would you prescribe?
- Ondansetron and dexamethasone
- **Prochlorperazine**
- Palonosetron, aprepitant, and dexamethasone
- Granisetron

Chemotherapy with Low Emetogenicity

NCCN Antiemesis Clinical Practice Guidelines: **Low** Emetogenic Chemotherapy

**Day 1 – Start before chemotherapy:
Repeat daily for fractionated doses of
chemotherapy**

- Dexamethasone 12 mg po/IV q.d.
or
- Metoclopramide 10-40 mg q 4-6hr prn
or
- Prochlorperazine 10 mg po/IV q 4-6 hr

- +/- Lorazepam 0.5-2 mg q 4-6 hrs
- +/- H2 blocker or proton pump inhibitor

Chemotherapy With Minimal Emetogenicity

NCCN Antiemesis Clinical Practice Guidelines: **Minimal** Emetogenic Chemotherapy

**Day 1 – Start before
chemotherapy:**

No routine prophylaxis

NCCN Antiemesis Clinical Practice Guidelines: **Anticipatory Nausea/Vomiting**

- Prevention with optimal antiemetics
- Behavioral therapy
 - Relaxation techniques
 - Guided imagery
 - Music therapy
- Acupuncture/acupressure
- Alprazolam 0.5-2 mg po on night before and morning of treatment
- Lorezepam 0.5-2 mg po on night before and morning of treatment

NCCN Antiemesis Clinical Practice Guidelines:
Breakthrough Therapy

Give an additional agent from another drug class

- Prochlorperazine
- Promethazine
- Metoclopramide
- Haloperidol
- Lorazepam
- Dolasetron
- Ondansetron
- Granisetron

NCCN Antiemesis Clinical Practice Guidelines:
Breakthrough Therapy

- Dronabinol
- Nabilone
- Dexamethasone
- Olanzapine

NCCN Antiemesis Clinical Practice Guidelines: Multi-Day Chemotherapy Regimens

- Overlapping acute and delayed emesis potential
- Cover the patient for every day of therapy, and an additional 3 days afterwards
 - Dexamethasone
 - Serotonin antagonist
 - Palonosetron q 3 days (not tested in this setting, but likely to be safe)
 - Aprepitant- Continue 80 mg qd dosing (not tested in this setting for efficacy, but safety is OK)

Principles of Emesis Control

- Prevention is the goal
- Risk of CINV lasts for at least 4 days for highly or moderately emetogenic chemotherapy
- Oral = IV
- Use lowest recommended dose

Penny Wise, Dollar Foolish?

- National Government Services (NGS)
 - Part A/Part B Medicare Administrative Contractor
 - January 13, 2009 – issued directive
 - If oral form of a drug is available, cannot use injectable form unless “medical necessity”
 - Documentation that patient could not tolerate the oral form
 - Oral meds usually are as effective
 - But.....

Penny Wise, Dollar Foolish?

- Many providers do not dispense oral drugs
 - Patients need to get their prescription filled at a pharmacy, bring it to clinic on the day of treatment
 - Some patients cannot afford the medication and so don't get it
- Physicians can only prescribe one cycle at a time
- Prior authorization, limits on quantities
- Non-compliant patients may do much better with intravenous drugs (don't have to remember to purchase and then take the oral antiemetic)

Anticipatory Nausea & Vomiting

- Poor initial experience with CINV leads to increased chance of N/V with subsequent cycles
- Our mandate: try to optimize the outcome with the first cycle of antiemetic treatment
- Historic precedent: NK1 inhibitors
 - Some patients do well with serotonin antagonists alone
 - Some hospitals mandated that this be tried first (less expensive); if bad outcome, add NK1 to the next cycle
 - Anticipatory N&V and more severe CINV can require I.V. fluids, more antiemetics, and even hospitalization

Conclusions

- CINV should be “prevented” aggressively with multi-drug regimens
- Guidelines are available and should be consulted
- Many institutions have generated pre-printed order sheets for uniformity and to insure standards of care are followed
- Steady improvements have been made in prevention of CINV
- Nausea prevention remains the biggest challenge



Thank You