3rd ASIA PACIFIC ONCOLOGY PHARMACY CONGRESS
7 – 9th July 2010

CHEMOTHERAPY INDUCED NAUSEA & VOMITING (CINV): WHAT'S NEW IN 2010?

National Cancer Centre Singapore
SingHealth

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Case 1

- Mr T.A.H, a 60 yr old man has been diagnosed with locally advanced Ca of the oropharynx
  - squamous cell carcinoma
  - T4a lesion with cervical node involvement
- He is currently receiving concurrent chemoradiation
- Today, he is due for his 2nd cycle of IV Cisplatin 100mg/m^2 (D1 only) chemotherapy
- How would you assess his risk for CINV?
- Given his previous CINV response, what modification(s) would you make to his antiemetic regimen ?

Case 2

- A 23 yr old male, S.T.H has been diagnosed with Stage III testicular cancer
- He is due for his 1st cycle of BEP chemotherapy regimen
  - IV Cisplatin 20mg/m^2/day (D1 to 5)
  - IV Etoposide 100mg/m^2/day (D1 to 5)
  - IV Bleomycin 15mg/day on Day 1 & Day 2
  - IV Bleomycin 30mg/day on Day 8 & 15
  - Every 21 days

Case 2

- Identify patient's risk factors for CINV
- What acute & delayed antiemetics would you recommend for him?

Objectives

- Review the pathophysiology of CINV
- Review the newer classes of antiemetics available
- To assess patient- and treatment-related CINV risk factors & to recommend appropriate prophylaxis &/or treatment of CINV

Concerns Associated with CINV

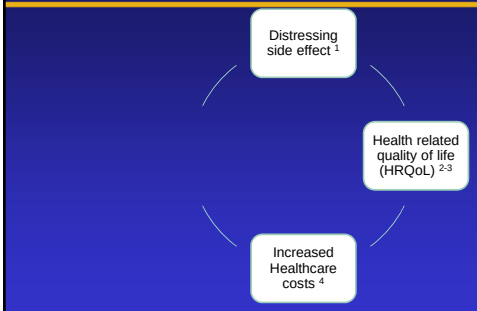
1. Coates et al. Eur J Cancer Clin Oncol 1983;19:203-8
2. Cohen L et al. Support Care Cancer 2007;15:497-503
3. Bloechl-Daum B et al. J Clin Oncol 2006;24:4472-8
4. Stewart DJ et al. J Clin Oncol 1999;17:344-51
5. Lindley CM, Hirsch JD. Br J Cancer Suppl 1992;19:S26-9

CINV – Most Feared Side Effect?

Ranking	1980's (Coates et al[1])	1995 (de Boer-Dennert M et al[2])	NCC In house study 2004 (not published)
First	Vomiting	Nausea	Vomiting / Thought of coming for treatment
Second	Nausea	Hair Loss	Damage to organs
Third	Hair Loss	Vomiting	Pain

1. Coates et al. Eur J Cancer Clin Oncol 1983;19:203-8
2. De-Boer-Dennert M et al. Br J Cancer 1997;76:1055-61

Concerns Associated with CINV



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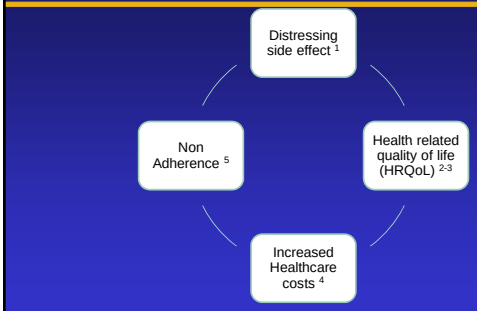
Increased Healthcare Costs

- Patients received moderate to highly emetogenic chemotherapy (n=2018)
  - 28% had uncontrolled CINV
- Average total direct medical cost per patient per month
  - Uncontrolled CINV costs US$1,300 more than controlled CINV group **(p<0.0001)**
- Average number of work loss days per month
  - Uncontrolled CINV group: 6.23 days vs
  - Controlled CINV group: 3.61 days (p=0.120)

Shih YC et al. Cancer 2007;110:678-85

Concerns Associated with CINV



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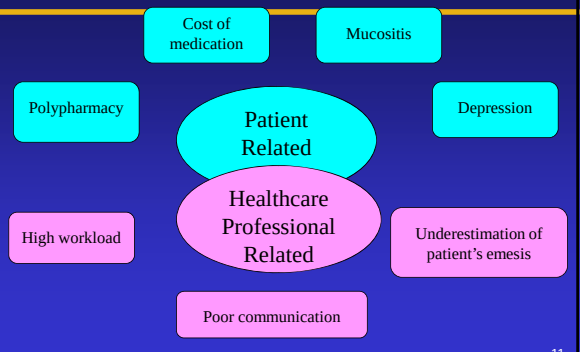
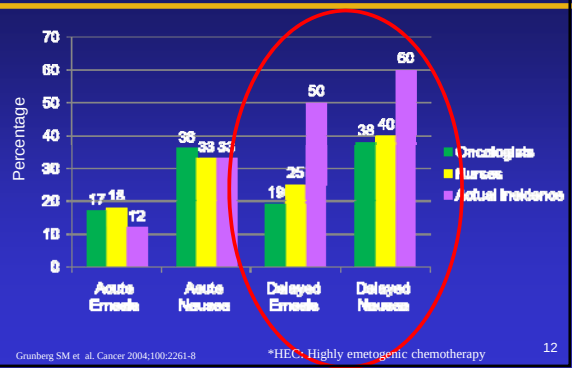
Barriers to Optimal Antiemetic Control



Grunberg SM et al. Support Care Cancer 2010;18(Suppl 1):S1-10

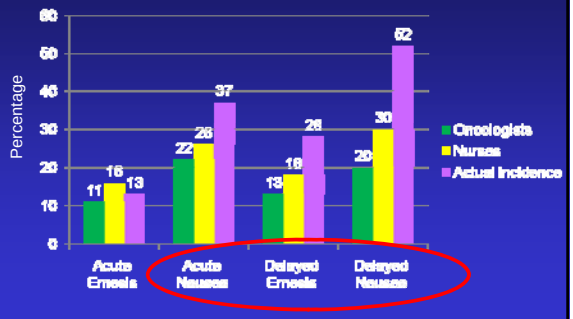
Oncologists' & Nurses' Predictions of Incidence of CINV vs Actual Incidence in HEC* Regimen



Grunberg SM et al. Cancer 2004;100:2261-8

*HEC: Highly emetogenic chemotherapy

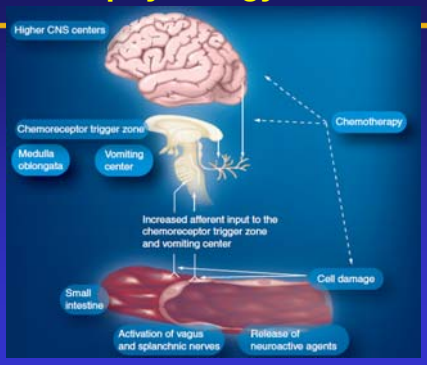
Oncologists' & Nurses' Predictions of Incidence of CINV vs Actual Incidence in MEC* Regimen



Grunberg SM et al. Cancer 2004;100:2261-8

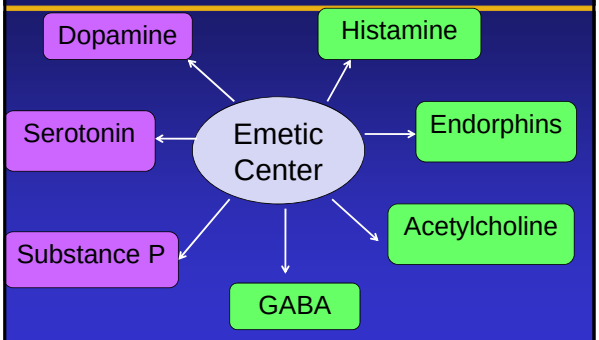
*MEC: Moderately emetogenic chemotherapy

Pathophysiology of CINV



Navari RM. Expert Rev Anticancer Ther 2008;8:1733-42

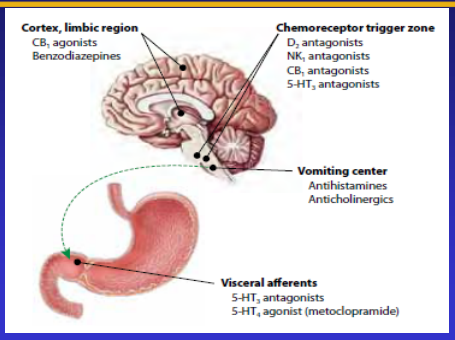
Neurotransmitters Involved in Emesis



Navari RM. Drugs 2009;69:515-33

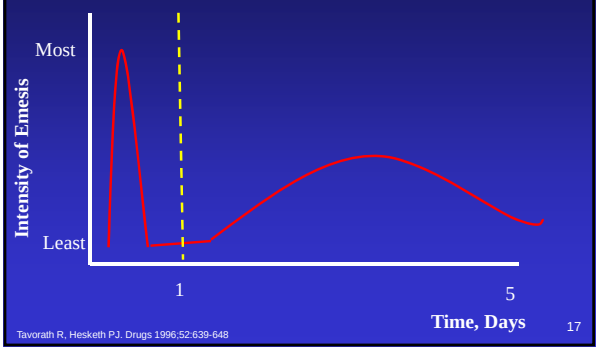
GABA: Gamma aminobutyric acid

Sites of Action of Different Classes of Antiemetics



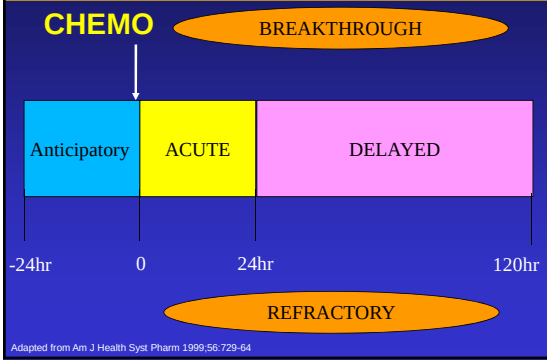
Frame DG. J Support Oncol 2010;8 (Suppl 1);5-9

Cisplatin Biphasic Pattern of CINV



Tavorath R, Hesketh PJ. Drugs 1996;52:639-648

Classification of CINV



Adapted from Am J Health Syst Pharm 1999;56:729-64

Emetic Risk of Chemotherapy Agents

High (>90%)	Moderate (30 – 90%)	Low (10 – 30%)	Minimal (<10%)
Cisplatin Streptozocin Cyclophosphamide ≥1,500mg/m^2 Carmustine Dacarbazine Dactinomycin	Oxaliplatin Cytarabine >1g/m^2 Carboplatin Ifosfamide Cyclophosphamide <1,500mg/m^2 Doxorubicin Daunorubicin Epirubicin Idarubicin Irinotecan	Paclitaxel Docetaxel Mitoxantrone Topotecan Etoposide Pemetrexed Methotrexate Gemcitabine Fluorouracil Trastuzumab	Bevacizumab Bleomycin Fludarabine Vinblastine Vincristine Vinorelbine

Kris MG et al. ASCO Guideline for Antiemetics in Oncology: Update. J Clin Oncol 2006;24:2932-47

Antiemetic Guidelines - ACUTE CINV

Emetogenicity of Chemotherapy	NCCN	ASCO
High (>90%)	NK1 receptor antagonist + Serotonin antagonist + Dexamethasone [+/- lorazepam (NCCN)]	
Moderate (30 – 90%)	Serotonin antagonist + Dexamethasone [+/- NK1 receptor antagonist / lorazepam]	
Low (10-30%)	Dexamethasone **OR** Any of the following Prochlorperazine, metoclopramide, &/or diphenhydramine &/or lorazapam	Low dose of dexamethasone
Minimal (<10%)	None	

Kris MG et al. ASCO Guideline for Antiemetics in Oncology: Update. J Clin Oncol 2006;24:2932-47
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemesis (v2 2010)

Antiemetic Guidelines - DELAYED CINV

Emetogenicity of Chemotherapy	NCCN	ASCO
High (>90%)	NK1 receptor antagonist (Days 2-3) + Dexamethasone (Days 2-4) [+/- lorazepam (NCCN)]	
Moderate (30 – 90%)	Any of the following NK1 receptor antagonist (Days 2-3) **OR** dexamethasone, serotonin antagonist, &/or lorazepam	Dexamethasone **OR** Serotonin antagonist (Days 2-3)
Low (10-30%)	None	
Minimal (<10%)	None	

Kris MG et al. ASCO Guideline for Antiemetics in Oncology: Update. J Clin Oncol 2006;24:2932-47
National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Antiemesis (v2 2010)

Limitations of Guidelines

- Do not incorporate patient's response to prophylactic antiemetics in previous treatment regimen & individual patient's risk factors
- Do not account for multiday chemotherapy regimens
- Do not account for CINV in regimens that contain multiple chemotherapy agents

CINV Risk Factors

- Treatment-related factors
  - Emetogenicity of chemotherapy regimen
- Patient-related factors
  - Age < 50 years
  - Female gender
  - Previous history of CINV
  - History of motion sickness
  - History of morning sickness
  - No significant alcohol intake
  - Anxiety

CINV Management – How are we doing now?

Historical Development of Antiemetics

Before 1980's
- **Phenothiazine / Dopamine Antagonists**
  - *Metoclopramide*

1990s
- **Serotonin ($5HT_3$) Antagonists**
  - *Granisetron (Kytril®), Ondansetron (Zofran®), Dolasetron (Anzemet®)*

2000s
- **Neurokinin-1 (NK1) Receptor Antagonists**
  - *Aprepitant (Emend®) (2003), Fosaprepitant (2008)*
- **Second Generation Serotonin ($5HT_3$) Antagonist**
  - *Palonosetron (Aloxi®) (2003)*
- **Transdermal Granisetron (Sancuso®)** (2008)

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NK1 Receptor Antagonist Aprepitant (Emend®)

- Used in combination with serotonin antagonist & corticosteroid to prevent CINV in moderate to highly emetogenic chemotherapy
- Available as oral capsules
- ~65% bioavailability, not affected by food
- Primarily eliminated via CYP3A4 pathway
  - Moderate inhibitor / inducer of CYP3A4
  - Inducer of CYP2C9

Emend Product Insert 2003
Sanchez R et al. Drug Metab Dispos 2004;32:1287-1292
Shadle CR et al. J Clin Pharmacol 2004;44:215-33

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Drug Interactions with Aprepitant

Agents	PK Effects on Aprepitant	PK effects on Concomitant Drug
Dexamethasone	None	↑ AUC 2.2 fold
CYP3A4 Inhibitors Diltiazem Ketoconazole	↑ AUC 2 fold ↑AUC ~5 fold ↑ $t_{1/2}$ 3 fold	↑ AUC 1.7 fold None
CYP3A4 Inducer Rifampicin	↓AUC 11 fold ↓ $t_{1/2}$ 3 fold	None
CYP3A4 substrate Midazolam	None	↑ AUC 2.3 to 3.3 fold
CYP2C9 substrate Warfarin	None	↓S-warfarin by 34% (Day 8) ↓ INR by 14% (Day 5)
Oral contraceptives Ethinyl Estradiol (EE)	None	↓AUC of EE by 19% (Day 10)

Curran MP & Robinson DM. Drugs 2009;69:1853-78

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Olanzapine vs Aprepitant for the Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV): A Randomized Phase III trial

ASCO 2010 Abstract #9020
Navari RM. Gray SE, Kerr C

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Olanzapine

- Blocks multiple neurotransmitters
  - $5HT_3$ & D_2 receptors
- Phase II trials[1-2] have shown its efficacy in preventing acute & delayed CINV
- Common side effect
  - Sedation, weight gain

1. Navari RM et al. Support Care Cancer 2005;13:529-534
2. Navari RM et al. Support Care Cancer 2007;15:1285-1291

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Olanzapine vs Aprepitant for the Prevention of CINV

- Randomized, Phase III trial
- Chemo-naïve patients receiving high emetogenic chemotherapy (cisplatin $\geq$ 70mg/m^2 or doxorubicin $\geq$ 50mg/m^2)

Treatment Arms	Acute Antiemetics	Delayed Antiemetics
Olanzapine	PO Olanzapine 10mg IV Palonosetron 0.25mg IV Dexamethasone 20mg	PO Olanzapine 10mg (Days 2 to 4)
Aprepitant	PO Aprepitant 125mg IV Palonosetron 0.25mg IV Dexamethasone 12mg	PO Aprepitant 80mg (Days 2-3) PO Dexamethasone 4mg bd (Days 2-3)

Navari RM et al. ASCO 2010 #9020

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Olanzapine vs Aprepitant for the Prevention of CINV

- N= 50 (29 females, 21 males)
- Median age= 58 yrs (39 – 81yrs)

	Acute Period (Day 1 post chemo)	Delayed period (Days 2 – 5 post chemo)	Overall (Day 1 to 5)
Complete response (CR) (%)			
Olanzapine (n=27)	100	75	75
Aprepitant (n=23)	87	70	70
Without Nausea (%)			
Olanzapine (n=27)	88	65	65
Aprepitant (n=23)	88	38	38

Navari RM et al. ASCO 2010 #9020

Fosaprepitant

- Water soluble prodrug of aprepitant (active)
- Converts to aprepitant within 30mins
- Fosaprepitant 115mg ≡ Aprepitant 125mg
- Dosing
  - Day 1: Fosaprepitant (IV) 115mg
  - Day 2 & 3: Aprepitant (PO) 80mg daily

Lasseter KC et al. J Clin Pharmacol 2007;47:834-40

Single dose Fosaprepitant for Prevention of Cisplatin-Induced NV

- Phase III, randomized, double blind, active control study (n=2247)
- Chemo-naïve patients on IV Cisplatin ≥70mg/m^2
- Treatment arms
  - Aprepitant [125mg (D1) & 80mg (D2 &3)]
  - IV Fosaprepitant 150mg (D1 only)

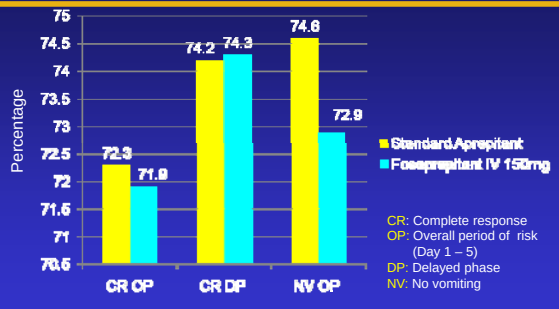
Grunberg SM et al. ASCO 2010 Abstract #9021

Single dose Fosaprepitant for Prevention of Cisplatin-Induced NV

- Primary endpoint
  - Complete response (CR) : No vomiting & no rescue medication during overall period (OP) of risk
- Secondary endpoints
  - Complete response during delayed phase (DP)
  - No vomiting (NV) during overall period

Grunberg SM et al. ASCO 2010 Abstract #9021

Single dose Fosaprepitant for Prevention of Cisplatin-Induced NV



CR: Complete response
OP: Overall period of risk (Day 1 – 5)
DP: Delayed phase
NV: No vomiting

Conclusion: Single day regimen of fosaprepitant was non inferior to standard 3 day regimen of aprepitant

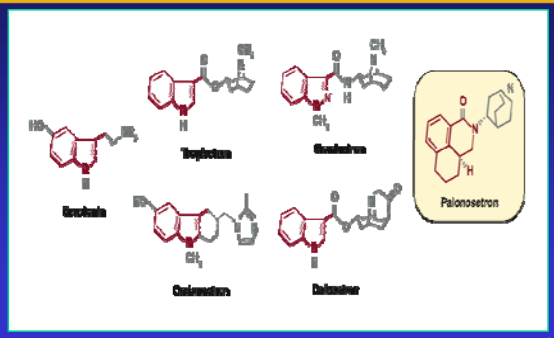
Grunberg SM
ASCO 2010 Abstract #9021

Casopitant (Rezonic™ / Zunrisa™)

- [Single oral dose (150mg) / 3 day IV & oral (90mg IV Day 1, 50mg oral on Day 2 & 3)] + Ondansetron + Dexamethasone
  - Reduces CINV events (p<0.05)
- Safety Issues
  - Administer with vinorelbine and etoposide
    - Grade 4 Neutropenia : 34% (Casopitant) vs 18% (Control)
- Application withdrawn in October 2009

Grunberg SM et al. Lancet Oncol 2009; 10:549-58

1st vs 2nd Generation Serotonin Antagonists



1st vs 2nd Generation Serotonin Antagonists

Drug (Brand Name)	Affinity for $5HT_3$ receptors (pKi)	Half lives (hrs)	Metabolism
Ondansetron (Zofran®)	8.39	4 – 6	CYP2D6, CYP3A4
Granisetron (Kytril®)	8.91	5 - 8	CYP3A4
Dolasetron (Anzemet®)	7.6	5-8	CYP2D6, CYP3A4
Palonosetron (Aloxi®)	10.45	~40	CYP2D6, CYP3A4

Tonini G et al. Expert Opin Drug Metab Toxicol 2005;1:143-9
Wong EH et al. Br J Pharmacol 1995;14:851-9
Clark RD et al. J Medicinal Chem 1993;36:2645-57

Palonosetron vs Ondansetron

Study	Design	Results			P value
			Palonosetron	Ondansetron	
Gralla et al [1] (2003) N=563	Phase III, double blind, randomized **Moderate** Emetogenic chemo	Complete response (CR) (1)Acute (2)Delayed (3)Overall (0-120hr)	 81% 74.1% 69.3%	 68.6% 55% 50.3%	< 0.01
Aapro et al[2] (2006) N=667	Phase III, double blind, randomized **High** Emetogenic chemo	Complete response(CR) (1)Acute (2) Delayed (3) Overall (0-120hr)	 64.7% 42% 40.7%	 55.8% 28.6% 25.2%	p < 0.05

1. Gralla R et al. Ann Oncol 2003:14:1570-7
2.Aapro MS et al. Ann Oncol 2006;17:1441-9

Palonosetron – ASCO 2010

- CINV associated hospital & ER visits in real practice: Palonosetron vs other $5HT_3$ antiemetic regimens (Abstract #9127)
- Randomized pharmacokinetic evaluation of subcutaneous vs intravenous palonosetron in cancer patients treated with platinum-based chemotherapy (Abstract #e19514)

New Delivery Option Transdermal Granisetron (Sancuso®)

- Indication: Prevention of CINV in patients receiving HEC / MEC for up to 5 consecutive days
- Each patch contains 34.3mg of granisetron (~ 3.3mg of drug delivered daily)

Sancuso® Product Insert 2008

Transdermal Granisetron (Sancuso®)

- Randomized, active control, double dummy, parallel group, Phase III trial (n=582)
- Pts received 3 to 5 day regimens of moderate to highly emetogenic chemotherapy
- Treatment arms
  - Transdermal granisetron (24-48hrs before chemo) vs
  - Oral granisetron (1 hr before chemo)
- Complete control
  - 60.2% (transdermal) vs 64.8% (oral) (p>0.05)

Grunberg SM et al. MASCC 2007

Transdermal Granisetron (Sancuso®)

- Administration
  - Apply to clean, dry, intact skin on upper outer arm
  - 24 to 48hrs before chemotherapy & removed a minimum of 24 hrs after completion of chemotherapy
  - Can be worn up to 7 days
  - Avoid direct exposure of application site to natural or artificial sunlight while wearing patch & for 10 days after removal

Transdermal Granisetron (Sancuso®)

- Advantages
  - Convenience (esp for multiday chemo)
  - Better adherence
- Disadvantages
  - Receive unnecessary dose of medication if chemotherapy cancelled at the last minute
  - Possible local skin irritation

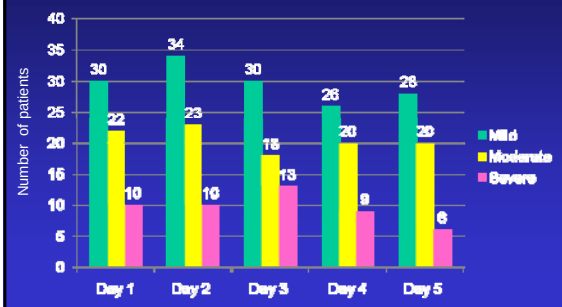
CINV Research at NCC

Clinical Predictors of CINV in Breast Cancer Patients Receiving Adjuvant Doxorubicin & Cyclophosphamide

		Motion Sickness		History of Chemotx Induced Nausea	
Age, years		No	89%	No	11%
<50	52%	Yes	11%	Yes	37%
>50	48%			NA	52%
Race		Morning Sickness		History of Chemotx Induced Vomiting	
Chinese	90%	No	60%	No	29%
Malay	5%	Yes	36%	Yes	19%
Indian	2%	NA	3%	NA	52%
Other	2%				
		Anxiety		Alcohol Usage	
		No	59%	None	90%
		Yes	41%	Social	10%

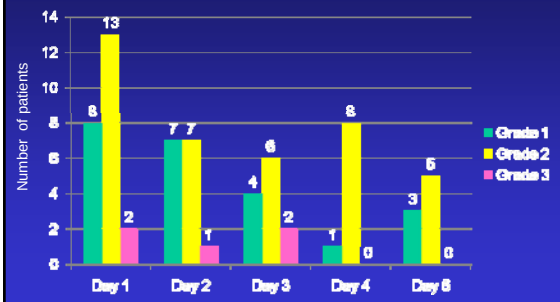
Shih V et al. Ann Pharmacother. 2009;43:444-52

Incidence of Nausea (n=91)



Shih V et al. Ann Pharmacother. 2009;43:444-52

Incidence of Emesis (n=91)



Shih V et al. Ann Pharmacother. 2009;43:444-52

How do Asians Measure Up?

	Warr et al (N=856)	Chan et al (N=244)	
	Overall Emesis	**Acute Emesis**	**Delayed Emesis**
Predictors	*p* value	*p* value	*p* value
Young age	**0.006**	**0.02**	NS
Alcohol History (+)	**0.0048**	NS	NS
Morning Sickness (+)	**0.0007**	NS	NS
Motion Sickness (+)	NS	**0.02**	**0.02**
History of chemotherapy-induced emesis	NA	**0.02**	**0.04**

Warr et al. MASCC Abstract 2009
Chan et al. ASCO Abstract 2010

NS = Not statistically significant
NA= Not available

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Case 1

- Mr T.A.H, a 60 yr old man has been diagnosed with locally advanced Ca of the oropharynx
  - squamous cell carcinoma
  - T4a lesion with cervical node involvement
- He is currently receiving concurrent chemoradiation
- Today, he is due for his 2nd cycle of IV Cisplatin 100mg/m^2 (D1 only) chemotherapy
- How would you assess his risk for CINV?
- Given his previous CINV response, what modification(s) would you make to his antiemetic regimen ?

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Case 1

- Upon assessment of patient, you retrieve the following information
- Medical history
  - Childhood asthma (last attack in his teens)
  - Diabetes (since 2007, on metformin 1g bd, last HbA1c 7.3%)
- Social history
  - Does not smoke or drink alcohol

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Case 1

- Cycle 1 CINV response
- Vomitted
- Day 1: 3 times
- Day 2 – 4: 2 times each day
- Nausea
- Day 1: rated 3/10
- Day 2 – 3: rated 6/10
- Day 4: rated 4/10

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Case 1

- Acute antiemetic prescribed for C1
  - PO Aprepitant 125mg
  - IV Dexamethasone 8mg
- Delayed antiemetic prescribed
  - PO Aprepitant 80mg (D2 & 3)
  - PO Dexamethasone 4mg bd (D2-4)
  - PO Metoclopramide 20mg qds prn
- He now c/o of dry mouth & odynophagia
- What antiemetics would you recommend for him for his 2nd cycle of chemotherapy?

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Case 1

- Risk factor assessment
  - Highly emetogenic regimen
  - History of CINV
  - Non alcohol drinker
- Adherence to antiemetics
  - If non adherent – reason(s)?

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Case 1

- Recommendation
- Acute
  - Fosaprepitant?
  - Transdermal granisetron?
  - Palonosetron?
- Delayed
  - Lorazepam?
  - Olanzapine?

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Case 2

- A 23 yr old male, S.T.H has been diagnosed with Stage III testicular cancer
- He is due for his 1st cycle of BEP chemotherapy regimen
  - IV Cisplatin 20mg/m^2/day (D1 to 5)
  - IV Etoposide 100mg/m^2/day (D1 to 5)
  - IV Bleomycin 15mg/day on Day 1 & Day 2
  - IV Bleomycin 30mg/day on Day 8 & 15
  - Every 21 days

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Case 2

- Identify patient's risk factors for CINV
- What acute & delayed antiemetics would you recommend for him?

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Case 2

- Medical History
  - Allergic rhinitis
  - History of motion sickness
- Social History
  - Social drinker
  - Non smoker
- His mother was informed by relatives that ginger tea / adding ginger to his diet might help with his CINV. She asked if it was truly effective & would you recommend it?

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Case 2

- Assessment of CINV risk factors
- *√Highly emetogenic regimen*
- *√Young (23 yrs old)*
- X Male
- X Chemo naïve
- *√History of motion sickness*
- ~ Social drinker

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Case 2

- Acute antiemetics
- NK1 receptor antagonist +
- Serotonin antagonist
  - 1st generation vs 2nd generation vs transdermal granisetron
- Dexamethasone

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Case 2

- Delayed antiemetics
- NK1 receptor antagonist (D2-3)
- Dexamethasone (D2-D4)
- Dopamine antagonist (prn)
- Benzodiazepines?

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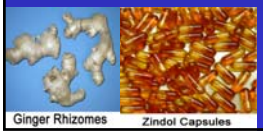
Case 2

- Query on ginger
  - May need to take a substantial amount
  - Daily dose of **0.5g to 1g** shown to significantly aid in the reduction of nausea during the **1st day** of chemotherapy (ASCO 2009 Abstract #9511)



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General Points to Consider

- Drug allergy
- Medical history
- Adherence to medication
- Preferred route of administration
- Previous experience with antiemetics
  - Effective?
  - Side effects experienced?
- Onset & duration of CINV
- Cost

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PATIENT ASSESSMENT IS CRUCIAL!

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Patient Care Guidelines

Patient scheduled for chemotherapy

Assess the need for CINV prophylaxis
(1) Is patient at **HIGH risk** for CINV?
(2) Patient's **history of emesis with previous chemotherapy**?
(3) What is the **emetogenic potential** of the planned chemotherapy regimen?
(For multi-drug regimens, select antiemetic therapy based on the drug with the highest emetic risk)

(1) Start **APPROPRIATE prophylaxis** (patient-specific risk factors & emetic potential of chemotherapy prior to chemotherapy)
(2) Patients with **anticipatory emesis: PRETREAT with behavioural therapy** or anxiolytics on evening before chemotherapy
(3) All prophylaxis regimens can be augmented with lorazepam &/or histamine H2 receptor antagonist as required

Drugs & Therapy Perspectives 2009;25:17-21

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Patient Care Guidelines

Administer appropriate prophylaxis based on emetogenic potential of chemotherapy

Breakthrough Emesis / Nausea occurs

Administer **ADDITIONAL** agent from **DIFFERENT** drug class (eg prochlorperazine, metoclopramide,lorazepam)

Emesis / Nausea controlled?

YES → Continue breakthrough medications **on a schedule** (not as required)

NO → Consider **changing** antiemetic therapy to **higher level primary treatment**

Drugs & Therapy Perspectives 2009;25:17-21

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Future Challenges…

- To aim to achieve better control of nausea
- To be able to come up with a more simplified antiemetic regimen
- Novel delivery methods for antiemetics
- To develop validated predictive tool for assessment of CINV

PREVENTION IS STILL THE KEY!