Why Do We Need Another Antiemetic? Just Ask

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Why Do We Need Another Antiemetic? Just Ask

- Physiology of vomiting
- Development of antiemetic drugs
- Antiemetic Guidelines
- Is emesis an issue in 2004?
- Aprepitant - NK-1 antagonist
- Palonosetron – a $5HT_3$ antagonist

Emesis

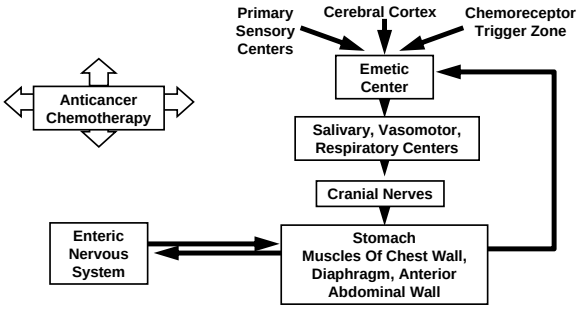
- Barf
- Blow chunks
- Blow doughnuts
- Blow groceries
- Blow lunch
- Boot
- Buick
- Chunder
- Drive the porcelain bus
- Heave
- Hurl
- Instant boot camp
- Kiss the porcelain god(dess)
- Lose lunch
- Lose your doughnuts
- Puke
- Ralph
- The technicolor yawn
- Toss your cookies
- Toss your tacos
- Throw up
- Upchuck
- Vomickin
- Woof

Effects of Chemotherapy Patients Fear Most

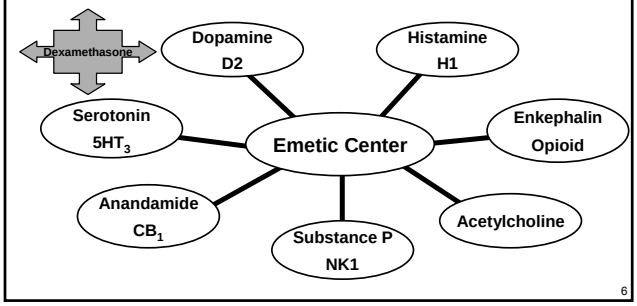
1. Vomiting
2. Nausea
3. Loss of hair
4. Coming for treatment
5. Treatment duration
6. Hypodermic injection
7. Shortness of breath
8. Constantly tired
9. Difficulty sleeping
10. Effects on family or partner
11. Effects on work/home duties
12. Parking
13. Feeling anxious or tense
14. Feeling low or depressed
15. Loss of weight

Coates A. Eur J Cancer 1983;19:203

Chemotherapy Induced Vomiting



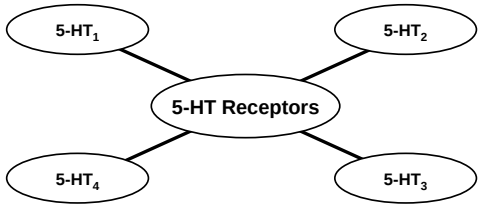
Neurotransmitters and Receptors Found in the Emetic Center



Causes of Vomiting in Persons with Cancer

- Chemotherapy-related
  - acute (0-24 h after chemotherapy)
  - delayed (>24 h after chemotherapy)
  - anticipatory (before chemotherapy)
- Not Chemotherapy-related
  - radiation
  - metastases – brain and GI tract
  - other causes, especially narcotic analgesics and antibiotics
  - multifactorial

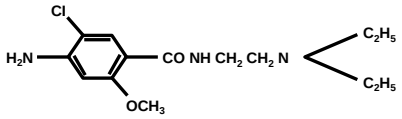
Serotonin (5-HT) Receptor Subtypes



5-HT_3 Antagonist Antiemetics

- Metoclopramide (Reglan™)
- Ondansetron (Zofran™)
- Granisetron (Kytril™)
- Dolasetron (Anzemet™)
- Palonosetron (Aloxi™)

Metoclopramide (Reglan™)



1964 Anti-Emetic. Effective against apomorphine or copper sulfate. Gastric motility stimulant.

1968 Sensitization of gastric smooth muscle and enhancement of cholinergic activity.

1970 Blocks 5-HT neuronal receptors in guinea-pig colon.

1973 Blocks 5-HT 'M' receptors (now 5-HT_3) in guinea-pig ileum.

1975 Blocks dopamine receptors.

1981 High doses inhibit cisplatin-induced emesis in man.

Initial Trials With Metoclopramide and Chemotherapy

Investigator	Dose (mg)	Chemotherapy	Conclusion for Metoclopramide
Moertel	20 x 3	Various	Ineffective
Khan	20 x 1	Cisplatin	92% antiemetic control
Arnold	20 x 2	Cisplatin	Same as prochlorperazine
Frytak	20 x 3	Cisplatin	Superior to prochlorperazine overall effectiveness poor
Belt	20 x 3	Cisplatin	Same as prochlorperazine

Plan Of Agent Development

- Phase I — Establish safety and MTD (maximal tolerated dose)
  Phase II — Efficacy with specific chemotherapy agents
- Phase III — Compare against standard therapies
- Dose-Response Studies — Optimize dose
- Trials for Special Emetic Problems — Delayed emesis; Consecutive-day cisplatin

Phase I Trial Of Intravenous Metoclopramide with High Doses of Cisplatin

Dose (mg/kg)	N	Sedation	Diarrhea	Extrapyramidal
0.40	8	3	1	0
0.50	3	1	1	0
0.60	5	0	2	0
0.70	2	0	1	0
0.85	7	0	1	0
1.0	3	1	2	0
1.3	6	0	3	0
1.75	3	0	1	0
2.33	5	1	2	0
3.0	4	0	2	0

Gralla RJ in Poster, Ed 1979

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Antiemetic Trial Design

- Dosage and schedule defined in Phase I Trials
- Standard emetic stimulus
- No prior chemotherapy
- Standard methods of assessment

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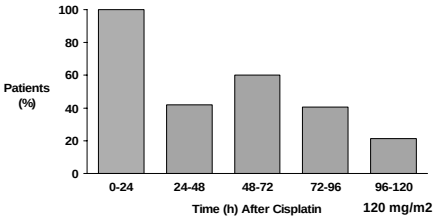
The Gold Standard Emetic High Dose Cisplatin



Gralla RJ. N Engl J Med 1981, Kris MG. J Clin Oncol 1985

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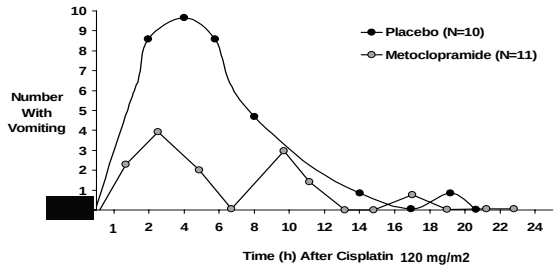
Time Course of Vomiting After High Dose Cisplatin



Gralla RJ. N Engl J Med 1981

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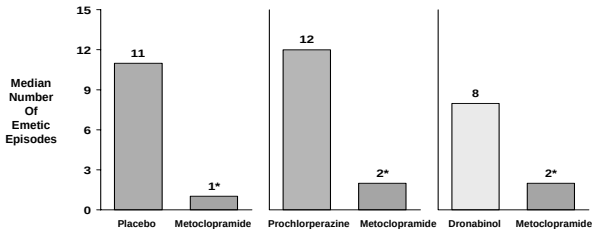
Efficacy of IV Metoclopramide Following High Dose Cisplatin



Metoclopramide 2 mg/kg IV × 5; prochlorperazine 10 mg IM × 5; dronabinol (THC) 10 mg/m^2* Cisplatin Dose 120 mg/m^2 *P*<.005

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Inhibition of Cisplatin-Induced Vomiting By Selective 5-Hydroxytryptamine M-Receptor Antagonism

Wesley D. Miner & Gareth J. Sanger
Beecham Pharmaceuticals Research Division

"MDL 72222, the selective 5-hydroxytryptamine (5-HT) M-receptor antagonist, prevented or reduced cisplatin-induced emesis in ferrets. It is suggested that cisplatin-induced, and possibly other cytotoxic drug-induced vomiting may involve a 5-HT M-receptor mechanism."

Br J Pharmacol 1988;88:497

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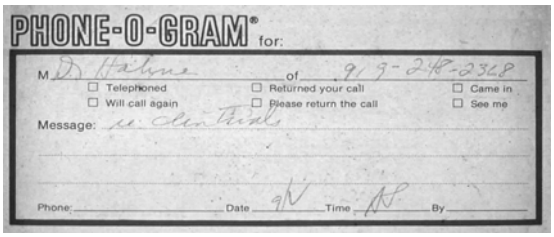
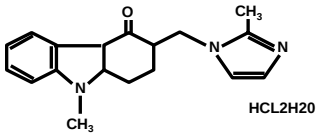
Message from Dr. William Hahne RE: New Glaxo Drug GR-C507/75 Received 2 SEPTEMBER 1986

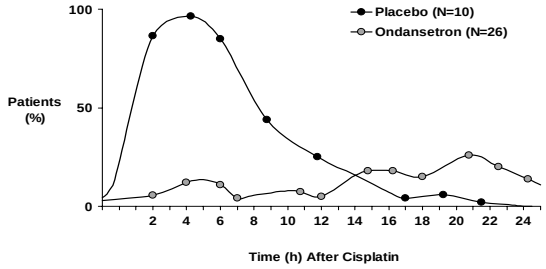


GR-C507/75 (Ondansetron, Zofran™)



- Selectively inhibits 5-HT_3 receptors
- Preclinical studies demonstrate control of cisplatin-induced emesis

Ondansetron Effect on Emesis After High Dose Cisplatin

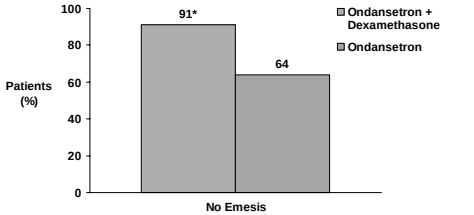


Kris MG. J Clin Oncol 1988; 6:659

Dexamethasone

- Mechanism of action unknown
- More effective than placebo and prochlorperazine in controlled trials
- Effective against vomiting caused by any chemotherapy and radiation
- No significant side effects when used at recommended doses and schedules
- No ↑ incidence of infections or change in frequency and site of metastases
- Inexpensive

Ondansetron Plus Dexamethasone Patients Given Cisplatin >50 mg/m²



Patients received ondansetron (0.15 mg/kg x 3) + dexamethasone (20 mg) *P*=.0005

Roila F. J Clin Oncol 1991;8:675

The Best Dose of Dexamethasone?

- Rx: Dexamethasone
- Indication: Acute emesis
- Patients: Cisplatin
- Results: All received ondansetron 8 mg IV
  Randomized to receive single IV doses

Dexamethasone	N	No Emesis	No Nausea
4 mg	133	69%	61%
8 mg	136	69%	61%
12 mg	130	79%	67%
20 mg	131	83%	71%

- Conclusions: No difference in adverse effects. Dexamethasone 20 mg should be the standard (20 vs 12 mg: 4% observed – 95% CI -5 to 14%)

The Italian Group. J Clin Oncol 2000

Lorazepam: A Good Drug to Add But Not As An Antiemetic

Lorazepam Dose	N	Patient Response (%) Major (0-2)	Minor (3-5)	Patients (%) Want More Lorazepam	Remember Chemotherapy
2 mg/m^2	10	0	40	100	20
1 mg/m^2	19	11	37	96	58
Total	29	7	38	97	45

Laszlo J. J Clin Oncol 1988

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Dronabinol (Marinol^{TM},THC)

- Active ingredient of Cannabis sativa, marijuana
- Superior to placebo and superior or equivalent to prochlorperazine in patients receiving mild and moderately emetogenic chemotherapies
- Inferior to metoclopramide with cisplatin
- Dizziness, ataxia, orthostatic hypotension, and dysphoria, particularly in older adults
- Oral formulation, approved for "patients who have failed to respond adequately to conventional antiemetic treatments"

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Delayed Emesis Definition

- Vomiting starting 24 or more hours after chemotherapy
- First defined with high doses of cisplatin & cyclophosphamide
- Mechanism unknown; may differ from acute emesis since drugs for acute emesis less effective here

Kris MG. J Clin Oncol 1985;3:1379

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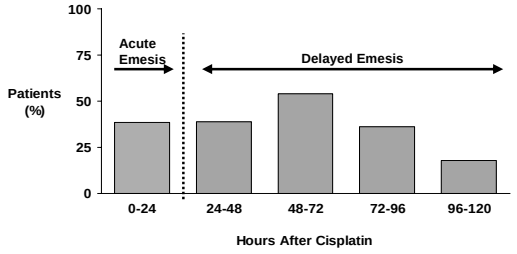
Delayed Emesis After High Dose Cisplatin With Antiemetics Given Only Pretreatment



Kris MG. J Clin Oncol 1985; 3:1379.

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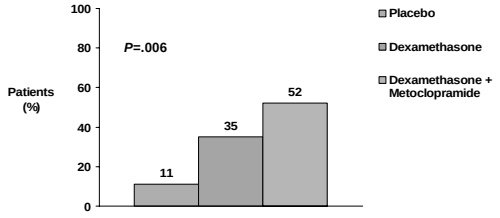
Delayed Emesis Random Assignment Trial



No Delayed Emesis between 24 and 120 hrs Following Cisplatin 120mg/m2

Kris MG. J Clin Oncol 1989

Delayed Vomiting Prevention High Dose Cisplatin – MSK Trials

Treatment	Delayed Vomiting Prevented
Placebo	11%
Ondansetron	15%
Dexamethasone	34%
Metoclopramide Dexamethasone	56%
Prochlorperazine Spansules + Dexamethasone	66%

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Delayed Emesis After Carboplatin, Anthracyclines or Cyclophosphamide

		Delayed Emesis
No Acute Emesis (n=618)	Placebo	23%
	DEX*	13%
	OND* + DEX	8%
Any Acute Emesis (n=87)	DEX	77%
	OND + DEX	59%

*Dexamethasone 4 mg 2xD + Ondansetron 8 mg 2xD; days 2-5

The Italian Group. NEJM 2000;342:1554

A Letter to the Editor in the NEJM

"The authors discuss a new agent for chemotherapy-induced emesis. The price of this drug for a 70-kg patient would be $115, which pays for the drug alone and not the intravenous diluents, administration sets and catheters. The actual charge to the patient could exceed $300. I am not suggesting that the use of a successful treatment should be based on cost, especially for this type of therapy. However, in the era of escalating health-care costs, the cost of drugs is a critical issue."

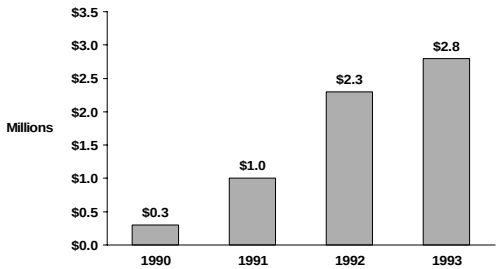
Nelson EA
Cost of Antiemetic Agents.
N Engl J Med 1982;307:225.

Ondansetron Introduction MSK Recommendations

Restrict ondansetron to labeled indication

- Days of chemotherapy only
- Prophylaxis only
- Always use with dexamethasone 20 mg
- No "PRN" use

Ondansetron Introduction Effect on MSK Drug Costs



Patient Charges for Oncology Drugs One Course or 4-Week Cycle

Dolasetron 100 mg PO	$ 45	Paclitaxel	$ 5802
Granisetron 2 mg PO	$ 150	Trastuzumab	$ 4941
Ondansetron 24 mg PO	$ 133	Zoledronic Acid	$ 995
Aprepitant 125/80/80 PO	$ 300		
Carboplatin	$2298	Timentin	$ 1618
Paclitaxel	$3868	Amikacin	$ 2300
Irinotecan	$7830	PEG Filgrastim	$ 3587
Gemcitabine	$5037	Epoetin alfa	$ 3296

Pharmacy Charges Only, July 2002
Based on 70 kg or 1.7 m^2 BSA

Step 1 in Guideline Development: Assess Ondansetron Use at MSK

- April 1993 - One week – 379 treatment days
- Emetic Risk of chemotherapy
  - 28% high (i.e., cisplatin ≥100 mg/m^2)
  - 44% moderate (i.e., CHOP)
  - 17% mild (i.e., CMF)
  - 11% minimal (i.e., 5FU)
- Dosing regimens:
  - 99% - 32 mg single dose or
    0.15 mg/kg × 2-3

Adjusting The Ondansetron Dose

Ondansetron Dose IV	Emesis Potential	No Emesis
32 mg*	**"High" (V)**	**74%**
24 mg*	**"Moderately High" (IV)**	**85%**
8 mg*	**"Moderate" (III)**	**88%**

***Dexamethasone 20 mg IV given to all patients.**

Hesketh P. J Clin Oncol 1995;13:2117

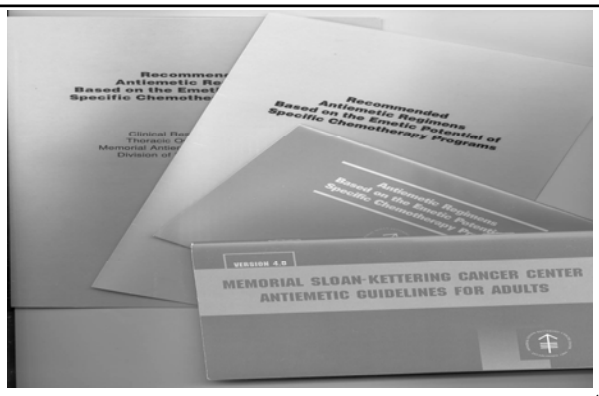
Guidelines For Serotonin Antagonist Use Step 2 - Implementation

- Restrict serotonin antagonists to "labeled" uses
- Create antiemetic committee: MDs, RNs, PharmDs
- Establish evidence-based, standard antiemetic regimens for each category of emetic risk
- Match antiemetic regimens and chemotherapy by emetic risk from literature and institutional experience of practice groups
- Obtain approvals and create a standard order: "Antiemetics per hospital guidelines"
- Check Box ….. Checked Box

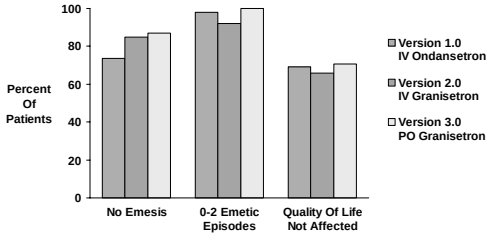
Nolte JM, J Clin Oncol 1999

MSK Antiemetic Guidelines Evolution

Version	Year	Chemo Regimens	
1.0	**1993**	**73**	**Adjusted-dose ondansetron**
2.0	**1994**	**86**	**IV granisetron**
3.0	**1995**	**172**	**Oral antiemetics**
4.0	**2000**	**211**	**Update**

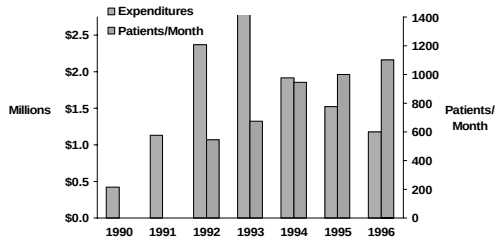


Vomiting Control With Guidelines Highly Emetogenic Chemotherapy MSK Quality Assurance Project



Nolte JM, J Clin Oncol 1999

MSK Antiemetic Guidelines
Antiemetic Costs vs Patients Treated



Nolte JM, J Clin Oncol 1999

Antiemetic Guidelines
A Partial List

- American Society of Clinical Oncology (ASCO)
- National Comprehensive Cancer Center Network (NCCN)
- American Society of Health System Pharmacists (ASHP)
- Multinational Association for Supportive Care in Cancer (MASCC)
- National Cancer Institute of Canada (NCIC)

Antiemetic Consensus Guidelines
Recommendations to Prevent Emesis

	Day 1 **Day of Chemotherapy**	**Days 2–4**
High	$5HT_3$ + Dexamethasone	Steroid + MCP *or*
	followed by ->	Steroid + $5HT_3$
Moderate	$5HT_3$ + Dexamethasone	Steroid alone:
	followed by ->	*or* + MCP / $5HT_3$
Low	Single agent	No preventive
	followed by ->	measures
Minimal	No preventive drugs	No preventive drugs

Prescribe medication for breakthrough emesis for all

Antiemetic Consensus Guidelines
Acute Emesis-Unanimous Agreement

- Dexamethasone should routinely be added to serotonin antagonists
- Lowest fully effective dose
- Oral equal to IV
- Equivalence of the serotonin antagonists (NOTE: May Change With MAR 2004 Update)
- Single prechemotherapy doses optimal

Side Effects Most Distressing to Patients Undergoing Emetogenic Chemotherapy

Identical Surveys Conducted Before and After the Availability of 5-HT_3 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 M et al. *Br J Cancer*. 1997;76:1057, © 1997, with permission from Cancer Research Campaign.

What Is The Incidence of Emesis Today?

- Cycle 1 Delayed Nausea & Vomiting
  - High Emetic Risk – 55%
  - Moderate Emetic Risk – 43%
- Guidelines Not Followed
  - High Emetic Risk - 57%
  - Moderate Emetic Risk – 36%

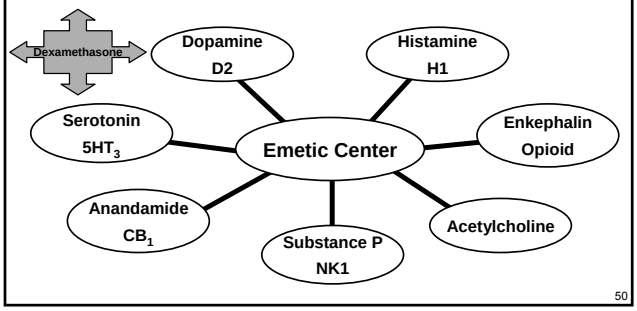
Fabi A. Support Care Cancer 2003; 11:156

Where We Succeed … Where We Fail

- Delayed Nausea
  - High Emetic Risk – 60%
  - Moderate Risk – 50%
- Acute Nausea
  - High Emetic Risk – 33%
  - Moderate Risk – 37%
- Delayed Emesis
  - High Emetic Risk – 50%
  - Moderate Risk – 28%
- Acute Emesis
  - High Emetic Risk – 11%
  - Moderate Risk – 13%

Grunberg Cancer 2004

Neurotransmitters and Receptors Found in the Emetic Center



Substance P – A Tachykinin

- An 11 amino acid regulatory peptide
- Found in the CNS (nucleus tractus solitarius & area postrema) &the GI tract
- Induces emesis in the ferret and dog
- Excites cholinergic neurons, causes vasodilitation, stimulates salivary secretion, contracts smooth muscle
- Binds to NK_1 receptor

Summary of Preclinical Evidence for NK-1 Antagonists

- NK-1 receptors found in brainstem emetic center and GI tract
- In animal models, NK-1 receptor antagonists demonstrate antiemetic activity against central, peripheral and combined emetic stimuli. Site of action is the CNS.
- Broad spectrum antiemetic activity in models unique among selective receptor antagonists
- Effective in delayed and acute emesis models

NK-1 Antagonists in Patients with Cancer

Development Ongoing	Development Halted
Aprepitant (Emend™, MK-869)	CJ-11,974
GW-597,599	GR-205,171
R-1124 (Ro-673189)	CP-122,721
	L-758,298

Phase I Trial of CP-122,721 An NK-1 Antagonist

- Cisplatin ≥100 mg/m^2
- Acute regimen: OND or GRA + DEX
- Study: 24 to 120 hrs
- One oral CP-122,721 dose before cisplatin
- Results:

	Entered	Acute Emesis Prevented	Delayed Emesis Prevented
CP-122,721	**17**	**65%**	**83%**

Kris MG. JNCI 1997; 89:53

Aprepitant (Emend™)

- An NK-1 receptor antagonist
- Given orally, once daily for 3 days
- Improves acute emesis control when given with dexamethasone and a $5HT_3$ receptor antagonist by 20%
- Improves delayed emesis control over placebo by 30%
- Approved in USA March 2003

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Aprepitant Triplet vs Std Doublet Regimens With Cisplatin >70 mg/m2

Day 1	Days 2 & 3	Day 4	
Ondansetron 32 mg IV			
Dexamethasone 12 mg PO	**Dexamethasone 8 mg PO**	**Dexamethasone mg PO**	**8**
Aprepitant 125 mg PO	**Aprepitant 80 mg PO**	**Dexamethasone and aprepitant placebos used throughout to maintain the double-blind design**	
Ondansetron 32 mg IV			
Dexamethasone 20 mg PO	**Dexamethasone 8 mg PO 2xD**	**Dexamethasone mg PO 2xD**	**8**

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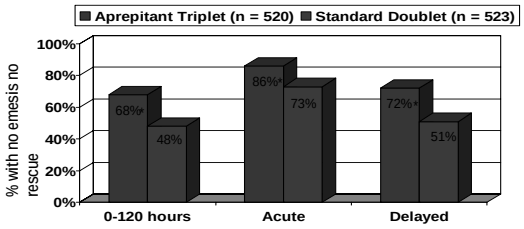
No Emesis and No Rescue Aprepitant Randomized Trials



All patients received initial cisplatin ≥ 70 mg/m^2

*p<0.001 compared to standard doublet for all comparisons

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IV Dolasetron vs IV Ondansetron Results in Women – Cisplatin ≥70 mg/m^2

	Emesis Prevented	
	Women	Men
Dolasetron	23%	53%
Ondansetron	27%	54%

Hesketh PH. J Clin Oncol 1996

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Aprepitant Triplet vs Std Doublet No Emesis and No Rescue Results in Women and Men

	Women	Men
Aprepitant Regimen	**66%**	**69%**
Standard Regimen	**41%**	**53%**

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Aprepitant (Emend™) What it is

- The first NK-1 receptor antagonist
- Given orally, once daily for 3 days
- Improves emesis prevention after cisplatin by 20% when given with dexamethasone and a $5HT_3$ receptor antagonist
- Improves the prevention of both acute and delayed phases of emesis
- Works equally well in men and women

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Aprepitant (Emend™) What it isn't

- A substitute for dexamethasone
- A substitute for a 5-HT_3 receptor antagonist
- A <u>treatment</u> for emesis of any kind

Palonosetron Aloxi™ (USA) – Onicit™ (Europe)

- 5-HT_3 antagonist antiemetic
- Half-life five times other agents
- Two log higher binding affinity
- Single IV dose pre-chemotherapy
- Activity in acute and delayed emesis
- Approved in USA July 2003

Palonosetron vs Ondansetron Moderate Emetic Risk Chemotherapy

Day 1	Days 2 & 3	Days 4 & 5
Palonosetron 0.25 mg IV	**None**	**None**
Palonosetron 0.75 mg IV	**None**	**None**
Ondansetron 32 mg IV	**None**	**None**

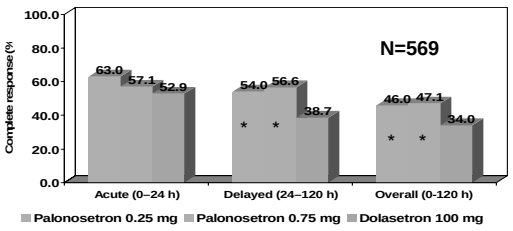
Gralla R Ann Oncol 2003;14:1570

Palonosetron vs Ondansetron Moderate Emetic Risk Chemotherapy

	Palonosetron 0.25 mg	Palonosetron 0.75 mg	Ondansetron 32 mg
Entered	**189**	**189**	**185**
Improvement with Palonosetron over Ondansetron – No Emesis or Rescue			
0-24 hours	**12% (2 to 23%)**	**5% (-6 to 16%)**	**X**
24-120 hours	**19% (8 to 30%)**	**10% (-2 to 21%)**	**X**

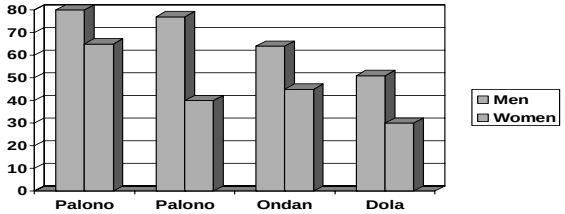
Gralla R Ann Oncol 2003; 14:1570 (n=563)

Palonosetron vs Dolasetron Moderate Emetic Risk Chemotherapy



*** *P* < 0.025** Eisenberg P Cancer 2003; 98:2473

5-HT_3 Antagonist Emesis Control Rates Moderate Emetic Risk Chemotherapy Results in Men vs Women



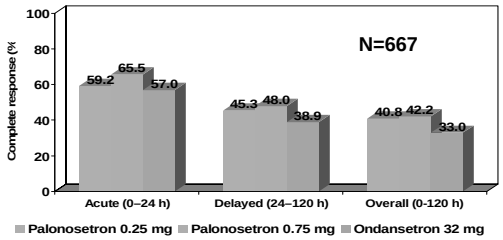
Gralla Ann Oncol 2003, Eisenberg Cancer 2003

Palonosetron-Dexamethasone-Aprepitant Phase II Trial

- Regimen
  - Palonosetron IV 0.25 mg day 1
  - Dexamethasone PO 12 mg d1, 8 mg d2, 3
  - Aprepitant PO 125 mg d1, 80 mg d2,3
- Patients
  - Receiving initial AC or Carbo/Paclitaxel (n=39)
- Results
  - 80% had no emesis or rescue 0-120 hrs

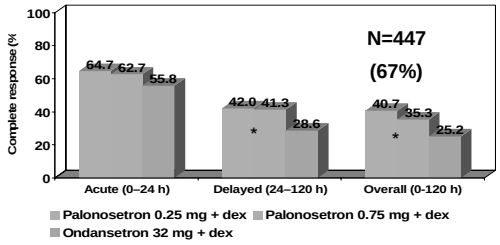
Grote Proc MASCC 2004

Palonosetron vs Ondansetron
High Emetic Risk Chemotherapy



Aapro M Support Care Cancer 2003:11:391.

Palonosetron vs Ondansetron
High Emetic Risk Chemotherapy
Patients Also Receiving Dexamethasone



***p* < 0.05** Aapro M Support Care Cancer 2003:11:391

Palonosetron
Aloxi™ (USA) – Onicit™ (Europe)
What it is

- 5-HT_3 antagonist antiemetic with a longer half-life and higher receptor binding affinity than similar drugs
- Given IV only once pre-chemotherapy
- Activity in acute and delayed emesis
- Phase III trials demonstrate better results than single agent dolasetron and ondansetron

Palonosetron
Aloxi™ (USA) – Onicit™ (Europe)
What it isn't

- A substitute for dexamethasone
- A substitute for aprepitant
- A <u>treatment</u> for emesis of any kind

Emetic Risk Groups
Representative Agents

High - Risk in 100%	**Cisplatin** **Dacarbazine** **Nitrogen mustard** **Cyclophosphamide/Doxoribicin**
Moderate - Risk in >30%	**Doxorubicin** **Carboplatin** **Cyclophosphamide**
Low - Risk in >10%	**Paclitaxel** **Etoposide** **Mitoxantrone**
Minimal - Risk <10%	**Chlorambucil** **Vinorelbine**

MGK Antiemetic Guidelines
Emetic Risk Categories/Recommendations

High and Moderate Emetic Risk	Palonosetron 0.25 mg IV day 1 Dexamethasone 12 mg PO days 1 - 4 Aprepitant 125 mg PO day 1 80 mg PO days 2 and 3

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MGK Antiemetic Guidelines
Emetic Risk Categories/Recommendations

Low	**Dexamethasone 12 mg PO**
Minimal	**PRN antiemetics only**

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Why Do We Need Another Antiemetic? Just Ask

- Persons with cancer still fear and experience vomiting and nausea with treatment
- Prevention is the goal of management
- Prescribe drug combinations for the entire time of risk
- Tap the power of guidelines
- Adding aprepitant improves acute and delayed emesis
- Palonosetron may be a better $5HT_3$ antagonist
- Research must continue until all nausea and vomiting associated with cancer are prevented

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