ANTIEMETIC GUIDELINES

These guidelines for adults are a summary of the knowledge updated from initial variant of June 1997. As this is a fluid field regular updates will occur as needed.

Regimens recommended because they minimize cost to patients whilst maintaining optimal control.

1st revision February 1999

The changes compared to June 1997 are:

1. The 5HT3 antagonists are interchangeable and which one is used should be based upon cost.

2. Recommended doses are: dolasetron 100 mg; granisetron 1 mg; or ondansetron 8 mg. The same dose is used whether the chemotherapy is highly or moderately emetogenic.

3. Same dose is used whether by the oral or intravenous route. Oral is the recommended route unless IV significantly cheaper (remember preparation time, IV fluid costs, etc.) or oral route contraindicated.

4. Decadron dose on day 1 is 12 mg not 8 mg, again by the oral route.

Individual chemotherapy protocols in the treatment manual will have a recommended antiemetic regimen included.

Detailed results demonstrating the evidence for the guidelines are presented in the appendices.

2nd revision October 2004

The changes compared to February 1999 are:

1. Decadron dose 8 mg (not 12 mg) pre chemo (Appendix 12)

*2. Palonosetron **may be** a superior 5HT3 antagonist on day 1 as its long half life (40 hrs) leads to less delayed emesis (Appendix 5/5a. Dose is 0.25 mg IV (no oral data)

3. NK1 receptor inhibitor "Aprepitant" improves both acute and delayed phase vomiting control due to:
   (a) both highly emetogenic and moderately emetogenic chemotherapy,
   (b) when available use routinely for highly emetogenic chemo and for moderately emetogenic at cycle 2 or greater if any vomiting with preceding cycle(s) (Appendix 15).
   (c) no need to reduce steroid dose as already using relatively low dose

* Not available in Canada as yet.

3rd revision November 2008

1. Single dose NK1 receptor inhibitor on day 1 [Aprepitant 125 mg or Casopitant 150 mg (discontinued) as good as a 3 day regimen [Appendix 17].

2. ASCO MASCC guidelines use NK1 receptor inhibitor routinely for "AC" breast chemotherapy. (No vomit over 5 days: 76% vs 59%. No vomit, minor nausea 51% vs 42%).

4th revision June 2011

1. Single dose IV Fosaprepitant 150 mg for those intolerant of oral route; single dose equivalent to 3 day aprepitant po

2. Casopitant development discontinued

5th revision September 2012

1. Palonosetron has Health Canada approval (March 2012)
   IV: 0.25 mg; po 0.5 mg po; po ≡ IV.

   Palonosetron provides superior delayed phase control compared to granisetron and by inference ondansetron.
   NB: No phase III data if aprepitant also used

2. Dolasetron no longer available

3. FDA warning re QT abnormalities – Ondansetron, granisetron, dolasetron (based on post marketing surveillance)

4. Anthracycline/cyclophosphamide containing breast cancer regimens moved to highly emetogenic category: still recommend using aprepitant as additional drug for prior cycle failures not a priori from cycle 1 (cost efficacy issue as cost high and absolute benefit small).

5. Olanazapine (very preliminary data) could replace aprepitant – cheaper ++++

6th revision August 2013

1. Palonestron marginally superior to granisetron (8% absolute benefit) in HEC in leading to no vomiting d2-5 (day 1 rates isq) when added to dex/aprepitant.

2. Dexamethasone use d2+3 gives slightly superior delayed phase outcomes versus use pre chemo only (absolute benefit, 4-9%) in combination with Palonestron (known delayed phase benefit, which may minimize absolute impact). (Appendix 5C). With HEC absolute benefit is 12% ($p < 0.02$)

3. Role for aprepitant in multiday platin based treatment.

7th revision December 2016 (Appendix 19)

1. Olanzapine decreases rates of nausea and emesis in early & late phases with HEC.
2. Sedation is a side effect – "severe" in 5%, effect wears off by day 3
3. Less vomiting with Olanzapine

8th revision December 2017

1. Serotonin syndrome [appendix 20]
2. Single day netupitant equivalent to 3 day aprepitant (appendix 17)
3. Netupitant/Palonestron as day 1, single pill has Health Canada NOC

December 2017
Paul Hoskins

ANTIEMETIC GUIDELINES FOR ADULTS (DECEMBER 2017)

STEP 1 **HOW EMETOGENIC IS THE CHEMOTHERAPY?**

HIGHLY/MODERATELY

THE REST → (1) no routine antiemetics
(2) +/- Prochlorperazine 10 mg or metoclopramide 10 mg as PRN medication or dexamethasone 8 mg po pre (ASCO 2011 guidelines)

STEP 2 **1st 24 HOURS***

60 mins pre chemo **NK1 inhibitor**

if **(1) Highly emetogenic; [includes AC for breast]**
or **(2) Vomiting with any cycle of mod emetogenic ie as "salvage"**

(a) use IV if oral route contraindicated or if cheaper than oral

(b) granisetron 1 mg or ondansetron 8 mg **or palonosetron 0.25 mg IV/0.5 mg po**

30 mins pre-chemo 5HT3 antagonist(a) po(b)
all pts to get: **dexamethasone 8 mg po**
12 hrs post chemo dexamethasone 4 mg po
Olanzapine 5-10 mg po (HEC or nausea with MEC)

STEP 3 **DELAYED PHASE (≥ 24**

HIGHLY	MODERATELY
Dexamethasone 4 mg po BID d2-5	Dexamethasone 4 mg po BID d2+3
** [**Aprepitant 80 mg po od d2+3]}**	**1)** Add NK1 inhibitor d1 or d1-3 if vomiting in any cycle as per highly emetogenic ***/**
Olanzapine 5-10 mg po od d2-5	2) Add Olanzapine if nausea occurs -cover nausea duration

NB: No role for routine use of 5HT3 antagonist in delayed phase (see Appendix 13)

* If a multiday regimen with same agents regard each day as if the "1st 24 hrs"
If vomit change to IV route; Aprepitants role. See Appendix 18

** Data that single dose day 1 NK1 receptor inhibitor [Aprepitant 125 mg po; netupitant 300mg; Casopitant 150 mg po] as good as 3 day regimen

*** Could instead switch 5HT3 antagonist to Palonestron but costs more versus single day aprepitant

INDEX

TREATMENT FAILURE – WHAT TO DO FOR THE NEXT CYCLE

- **Aim is no nausea or vomiting. Relatively easy to achieve for 1st 24 hours, not so easy after that.**
- **No clear strategies available so following are suggestions only, except for adding NK1 receptor inhibitor, when available**
- **What to do depends upon when the nausea and vomiting occurs and patients ability to tolerate the degree of emesis.**

(A) **VOMIT IN THE 1st 24 HOURS**

- **Add NKI inhibitor if not already on it**
- increase the dose of 5HT3 antagonist 3 fold as single dose

OR

- **If cyclophosphamide containing + emesis > 8 hrs give 2nd dose of ondansetron 8 mg at 8 hrs post-chemo or double initial dose of granisetron (2 mg)**

- start dexamethasone 4 mg po b.i.d. 24 hrs pre-chemo
- add prochlorperazine
- add lorazepam 1 mg sl or po pre-chemotherapy.

Then if no better

- nabilone 1 mg po q 12 hr

Then if no better

- can the chemo regimen be altered to a less emetogenic regimen
- give Rx as in-patient
- behavioral modification
- or can the patient cope with this level of emesis.

(B) **VOMIT AFTER 1st 24 HOURS**

a) nausea and vomiting once antiemetics stopped: continue original delayed phase regimen longer to cover the known duration of emesis plus one day.

b) nausea and vomiting despite antiemetics.

- switch to Palonosetron and/or **NKI inhibitor if not already on it (starting pre-chemotherapy)**
- add dimenhydrinate (Gravol^{R}) 100 mg po b.i.d. (alternate with the prochlorperazine 10 mg po BID: ie, a q6h program).
- Add lorazepam 1 mg S/L BID
- Add olanzapine (see appendix 16)

Then if no better

- add nabilone 1 mg po q12hr

Then if no better

- can the patient cope with this degree of nausea and vomiting
  if yes: continue
  [1] if no: modify chemotherapy regimen or schedule or treat as in-patient

(C) **ANTICIPATORY NAUSEA AND VOMITING**

- start dexamethasone 4 mg po b.i.d. 24 hrs before
- behavioral modification/relaxation techniques [2]
- lorazepam 1 mg sl q12h. Start day before treatment.

[1] Consult patient's oncologist or tumor group at this time.

(D) **NAUSEA**

- add olanzapine

APPENDIX 1

EMETOGENIC POTENTIAL OF CHEMOTHERAPY

HIGH (>90%)	MODERATE: HIGH MODERATE (60-90%)	MODERATE: LOW MODERATE (30-60%)	MINIMAL (0-30%)
Cisplatin >50 mg	Doxorubicin >40 mg	VP16 (Etoposide) iv	5 FU
Streptozocin	Epirubicin >75 mg	Cyclophosphamide <1 g	Fludarabine
* FFC	Cisplatin <50 mg	Methotrexate	Paclitaxel
* **FAC**	**Carboplatin**	**Doxorubicin <40 mg**	**Vincristine**
* **AC ± "OTHER"**	**Oxaliplatin**	**ARA-C**	**Bleomycin**
* EC ± OTHER	Nitrogen mustard >6 mg	Asparaginase	Busulfan
	Cyclophosphamide >1 g	Irinotecan	Vinblastine
	Mitomycin C		Thiotepa
	Nitrosourea		Gemcitabine
	Actinomycin D		Vinorelbine
	DTIC		Topotecan
	Bendamustine		VP16 po
MOPP	Ifosfamide	CMF	2CDA
	PROMACE	ACOP-12	Liposomal doxorubicin
	CHOP	VACOP	Methotrexate
	CAV		Pralatrexate
	ABVD		"targeted" therapies
	AC		Mitoxantrone

( ) % who will vomit if no antiemetic used
* Breast cancer protocols

POINTS

- as infusion time increases, emetogenicity decreases
- as dose increases, emetogenicity increases
- combination more emetogenic than single agent
- repeat cycles, anti-emetogenics less successful

- N+V in 2hrs: Doxo, nitrogen mustard.
- N+V in 2-4 hrs: most drugs
- N+V late (> 9 hrs): Cyclo
- Nausea > vomiting

* doses are mg/m^2

APPENDIX 2

SCOPE OF THE PROBLEM

(1) Acute N+V (1st 24 hrs) if given placebo

- Moderately
  - any nausea 83-92%
  - any vomiting 78-92%
- Highly
  - any nausea 100%
  - any vomiting 89-100% (mean = 11, r 5-25)

∴ NEED TO TREAT BOTH GROUPS

(2) Delayed N+V (>24 hrs) – if given placebo

	DAY 2	3	4	5	6
MODERATELY EMETOGENIC					
• any nausea (%)	54	37	18	25	15
• any vomiting (%)	32	24	11	6	3
HIGHLY EMETOGENIC					
• any nausea (%)	48	78	70	40	
• any vomiting (%)	53	57	42	29	12

∴ NEEDED DURATION OF THERAPY

- **moderately d2+3**
- **highly d2-5 inclusive**

APPENDIX 3

DAY 1 CONTROL: 5HT3 + STEROID MANDATORY

	— % No Vomit on Day 1 —			
	Placebo Rate	***Anti-5HT3***	***Anti-5HT3/Corticosteroid***	***# Studies***
Moderately	<20%	55 – 80%	67 – 97%	6*
Highly	<10%	39 – 64%	58 – 91%	8**

- In all studies 5HT3 antagonist/Corticosteroid better than anti-5HT3 alone
- "Failure" rates ME ≤ 20%
  HE ≤ 30%
- Less success re nausea (10 – 15% less good)
- Implications for the Future:

  Moderately emetogenic: not routinely add 3rd drug?
  Highly emetogenic: routinely add 3rd drug

* Italian Group 1995, Kirchner, Carmichael, Lofters, Dreschler, Hulstaert
** Sorbe, Smythe, Hesketh, Latreille, Bacchi, Roila, Garcia-del-muro, Chevalier

APPENDIX 4

COMPARATIVE TRIALS OF 5HT3 ANTAGONIST. HIGHLY EMETOGENIC. (1ST 24 HR NO VOMIT RATES)

Author	*Ondansetron*					*Granisetron*			*Dolasetron*		*Tropisetron*
	8 od	*8 tid*	*24 mg*	*32 mg*	*.15 mg/kg*	*3 mg od*	*10 μg/kg*	*40 μg/kg*	*1.8 mg/kg*	*2.4 mg/kg*	*5 mg*
Ruff	59%			51%		56%					
Park		46%				46%					
Navari					51%		47%	48%			
Roila	79%					80%					
Hesketh				50%					44%	46%	
Noble			89%			92%					
Martoni		68%				71%					
Gebbia			52%			49%					
Mantovani			82%			84%					73%
Italian	79%					80%					
Audhuy						48%			54%	47%	

Summary: No significant differences in any study

APPENDIX 5

COMPARATIVE TRIALS OF 5HT3 ANTAGONISTS. MODERATELY EMETOGENIC. CHEMOTHERAPY (1ST 24 HRS NO VOMIT RATES)

Author	*Ondansetron*						*Granisetron*				*Dolasetron*			*Palonosetron*	
	8 od	*8 bid*	*8 tid*	*16 mg*	*24 mg*	*32 mg*	*1 mg bid*	*2 mg*	*3 mg*	*10 μg/kg*	*100 mg*	*2.4 mg/kg*	*2.8 mg/kg*	*0.25 mg*	*0.75 mg*
[1]															
Perez						63%				58%					
Perez						73%		71%							
Fauser			76%										72%		
Gebbia				69%					67%						
Stewart			78%						81%						
Bonneterre					45%				52%						
Pion (po)		Isq					Isq								
Bonneterre		Isq			45%		Isq								
[2]															
*Rubenstein						69%								81%	74%
*Rubenstein											53%			63%	57%
Lofters						67%						57%			

[1] = no significant difference

[2] = significant difference

APPENDIX 5a

PALONOSETRON ± DAY 1 STEROIDS ONLY
(NO EMESIS RATES)

1. MEC

	(A)			(B)		
DRUG	PAL	PAL	ONDAN	PAL	PAL	DOLAS
DOSE	0.25 mg	0.75 mg	32	0.25 mg	0.75	100 mg
ROUTE	IV	IV	IV	IV	IV	IV
WHEN	- pre Rx, day 1 -			- pre Rx, day 1 -		
D1	81%	74%	69%	63%	57%	53%
D2-5	74%	65%	55%	54%	57%	39%

NB:
- steroid 5% (B)
- no delayed phase antiemetics used

2. HEC

	PAL	PAL	ONDAN
	0.25 IV	0.75 IV	32 mg IV
D1	59%	66%	57%
D2-5	45%	48%	39%

66% also received single dose dexamethasone pre-treatment

B=Eisenberg; A=Gralle; HEC=AAPRO

- **Overall: Palonosetron superior <u>but</u> no delayed phase antiemetics ie not current standard**

APPENDIX 5b

Palonestron versus Granisetron with "standard" Dexamethasone

HEC or adria/cyclo (breast: Saito)

	A	B
Pal	0.75 mg IV d1	Gran 40 μg/kg d1 IV
Dex	16 mg IV d1 + dex 2-3	Dex as in (A)
D1	75%	73%
D2-5	57%	45% ($p < 0.0001$)

- **Palonsetron is a superior 5HT3 antagonist re d2-5 control**

NB: No comparative data if aprepitant used

APPENDIX 5c

Palonestron plus either d1 or d1-3 dexamethasone

A. CELIO		A	B	
		Palo 0.25 mg IV d1	Palo 0.25 mg IV d1	
		DEX 8 mg IV d1	Dex 8 mg IV d1, 8 mg po x1 d2+3	
CR				
	D1	89%	84%	
	D2-5	69%	78%	(p=0.116)

B. AAPRO		A	B	
		Palo 0.25 mg IV d1	Palo 0.25 mg IV d1	
		Dex 8 mg IV d1	Dex 8 IV d1→ 4 mg bid po d2+3	
CR				
	D1	69%	68%	
	D2-5	62%	66%	(p=0.2)

- Trend is for superior control with d1-3 dexamethasone (4-9% difference)

C. COMBINED ANALYSIS A&B

	#	Dex d1 only	Dex d1-3	p
MEC	237	83%	89%	0.2
HEC	380	72%	84%	0.02

Endpoint: d2-5, no vomiting and nausea <25/100 on visual analogue scale

APPENDIX 5d

MEC	Oral or IV Palonestron		Grunberg	
	0.25 mg po	0.50 mg po	0.75 mg po	0.25 mg IV
D1	74%	76%	74%	70%
D2-5	59%	63%	60%	65%

(+ d1 dexamethasone)

- Oral 0.5 mg po ≡ 0.25 mg IV

APPENDIX 5e

HEC. Palonestron versus Granisetron in Triplet therapy Hashimoto

	#	CR d1	CR d2-5	
Pal + Aprep + Dex	414	92%	67%	p=0.014
Gran + Aprep + Dex	413	92%	59%	

APPENDIX 6

WHAT IS THE MOST COST EFFECTIVE DOSE OF DOLASETRON?
(1ST 24 Hrs. – No Vomit Rates)

	mg/kg					*mg*			
	0.6	***1.2***	***1.8***	***2.4***	***3.0***	***25***	***50***	***100***	***200***
Highly Emetogenic									
Harman	23%		48%						
Chevalier		48%	57%						
Thant	43%	62%	69%	52%	56%				
Thant	30%	30%	38%	36%	39%				
Audhuy			54%	47%					
Pendergrass	41%	50%	59%						
Kriss			24%	48%	52%				
Thant (8 pooled trials)	41%	50%	44-55%	43%	48%				
Moderately Emetogenic									
Fauser						45%	49%	60%	76%
Fauser		56%	64%						
Hesueth	72%	45%	87%	67%					
Hesueth			44%	46%					
Rusenstein						31%	41%	61%	59%
Grote						33%	49%	62%	70%
Rubenstein (3 pooled trials)						40%	54%	65%	73%

Summary:
- **1.8 mg/kg is optimal (70 kg man = 125 mg)**
- **100 = 200 statistically, but trend favors 200 mg**

} **So routinely use 100 mg**

APPENDIX 7

WHAT IS THE MOST COST EFFECTIVE DOSE OF GRANISETRON?
(No Vomit 1st 24 Hr, Rates)

	μg/kg						*mg*		
	2	***5***	***10***	***20***	***40***	***160***	***1***	***2***	***3***
[1] Highly Emetogenic									
Navari		18%	41%	40%	47%				
Kamanabrou					57%	59%			
Riviere	31%		62%		68%				
Perez		23%	48%	48%	44%				
Soukoup					57%	60%			
Martoni							90%		94%
Navari			47%		48%				
[2] Moderately Emetogenic									
Kamanabrou					75%	81%			
Smith					76%	81%			

Summary:
- **10 μg/kg is the optimal**
- **in practice therefore: 1 mg**

APPENDIX 8

WHAT IS THE MOST COST EFFECTIVE DOSE OF ONDANSETRON?
(1st 24 Hrs – No Vomit Rates)

	mg							
	0.15 mg/kg x3	***8 od***	***8 bid***	***8 tid***	***16***	***24***	***32***	***Infusion***
Highly Emetogenic								
Ruff		59%					51%	
Beck	51%	42%					58%	
Seynaeve	51%						53%	52%
Marty							72%	76%
Sylvester					Isq		Isq	
Navari	71%							74%
Pectasides		68%				70%		
Moderately Emetogenic								
*Dicato			83%	86%				
Kaizer			92%		82%			
**Beck (po)			61%	58%				
***Dipiro						72%	76%	
Beck	1 mg po tid ≡ 4 mg po tid ≡ 8 mg po tid							
Fraschini	1 mg po tid < 4 mg po tid < 8 mg po tid							

Summary:
- **do not need 32 mg**
- **8 mg od or bid is sufficient**

***** **cr/mr rate**
****** **3 day rates**
******* **20 mg not 24 mg**

APPENDIX 9

ORAL OR INTRAVENOUS ROUTE

- Oral bioavailability of ondansetron = 60% of intravenous route
- Response comparing oral and intravenous regimens (nonrandomized) are similar for cisplatin based chemotherapies.

Author	***Regimen***	***#***	***No Vomit***	***No Nausea***	***No N+V***
Kris	po dol 200/dex 20 po	75	76%		
Heron	po gran 1 mg bid/dex 12 iv	117			55%
Hesketh	IV ond 32/dex 20 iv	57	72%	51%	

n = nausea; v = vomit; dol = dolasetron; gran = granisetron;
ond = ondansetron

- Martin Historical control study in moderately emetogenic

granisetron 1 mg po + dexamethasone 12 mg po
versus
ondansetron 10 mg iv + dexamethasone 10 mg po

Nausea & vomiting Rates Isq

- Stewart Moderately emetogenic randomized

		No vomit
[A]	ond 8 mg IV pre + po bid post	78%
[B]	ond 8 mg po pre + po bid post	78%

SUMMARY: Oral likely as good as intravenous
∴ use ∝ cost drug; nursing/pharmacy time; supplies
∝ convenience
∝ inability to take orally *

* suppository in testing; "dissolve on tongue capsule" of ondansetron available

APPENDIX 10

HIGHLY EMETOGENIC CHEMOTHERAPY: SINGLE DOSE VS. MULTIPLE DOSES

				— dl —		
Author	***Chemo***	***#***	***Regimen***	***^0V***	***^0N***	***^0N+V***
[A] Single Dose						
Pectasides	DDP ≥ 80	38	Dex 20 IV + Ond 8 IV	68%	61%	
Italian Group	DDP ≥ 50	322	Dex 20 IV + Ond 8 IV	78%	70%	65%
Italian Group	DDP ≥ 50	483	Dex 20 IV + Ond 8 IV	79%	72%	67%
Olver	DDP ≥ 70	640	Dex 20 IV + Ond 8 IV	81%		68%
Gridelli	DDP ≥ 50	236	Dex 20 IV + Ond 8 IV	80%		
[B] Multiple Dose						
Bacchi	DDP ≥ 50	53	Dex 20 IV + Ond 8 IV tid	81%		
Hesketh	DDP ≥ 100	127	Dex 20 IV + Ond 0.15 mg/kgx3	61%		
Hesketh	DDP ≥ 70	53	Dex 20 IV + Ond 32x1	72%	81%	
Smyth		84	Dex 20 IV + Ond 8 then infusion	58%	52%	
Franchi	DDP 40-80	58	Dex 16 IV + Ond 8 tid			
Italian Group	DDP ≥ 50	136	Dex 20 IV + Ond 0.15x3	79%	77%	

Summary: Single dose of ondansetron 8 mg plus steroid is as good as multiple doses of ondansetron.

DOP = cisplatin ^{0}v = no vomit ^{0}n = no nausea

APPENDIX 11

MODERATELY EMETOGENIC: SINGLE DOSE ONDANSETRON VS. "LONGER 5HT3"*

	Author	#	*Regimen*	*Chemo*	— *dl* — ^0V	^0N	^0N+V
[1] Single Dose							
	Hesketh	54		Dex 20 + Ond 8	88%	69%	
	Martin		MEC	Dex 10 + Ond 10	90%	73%	
	Perez	543	FAC/AC	"± Dex" + Ond 20	74%	60%	60%
	Perez		FAC/FEC	"± Dex" + Ond 32	63%	49%	
[2] Multiple Dose							
	Bonneterre	35	FAC/FEC	Dex 4 + Ond 4 → 8 tid	86%	75%	
	Soukop	93	Cyclo > 500	Dex 16 + Ond 8 → 8 tid	91%		
	Lofters		Cyclo or DDP	Dex 8 + Ond 8 bid	"75%"		
[3] Long Acting 5HT3							
	Lofters		Cyclo + DDP	Dex 8 +Dol 2.8	67%		
	Dreschler	60	Platinum	Dex20 + Trop 5	97%		
	Hulstaert	56	Breast/Lung	Dex + Trop	76%		
	Italian Group	135	Breast/Lung	Dex 8 + Gran 3	93%		
	Carmichael	141	Breast/Lung	Dex 8 + Gran 3	85%		
	Kirchner	111	Lung/Lymph	Dex 20 + Gran 3	81%		
	Silva	64	Breast	Dex12 + Gran 3	95%	73%	

Summary: No convincing data of a need for more doses nor for using a longer acting 5HT3

*Comparative information not randomized comparisons (^{0}n = no nausea, ^{0}v = no vomiting)

APPENDIX 12

OPTIMAL DOSE OF CORTICOSTEROID ON DAY 1

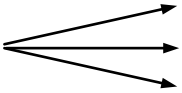
RATIONALE

- Corticosteroids are nasty drugs: short-term S/E (good + bad) and long-term: avascular necrosis

  ∴ Use the lowest effective dose

EVIDENCE

- Two randomized trials



Roila 1998 (Highly emeto)	8 mg IV	69% no vomit
	12 mg IV	78% no vomit
	20 mg IV	83% no vomit
Roila 2003 (Mod emeto)	8 mg IV	89% no vomit
	24 mg IV	84% no vomit
	8 mg IV + 4 mg po q6h x4	85% no vomit

- In practice doses used: 8-20 mg x 1, IV or po (day 1)

  Moderately emetogenic (non-randomized comparisons)

8 mg IV/po:	75% - 93%
20 mg IV:	80% - 97%

  Highly emetogenic (non-randomized comparisons)

NCIC study 10 mg IV:	64% no vomit
"Others" 20 mg IV:	68 – 80% rate

SUMMARY:

- **Dexamethasone 8 mg is as good as higher dose and minimizes potential for side effects (Jan 2004)**

APPENDIX 13

DELAYED PHASE – BEST Rx SO FAR (NO VOMIT RATES FROM DAY 2 ONWARDS)

		Placebo	*Anti-5HT3*	*Dexameth*	*Both*	*'P' Value*
[1] Moderately Emetogenic						
	Koo	33%		56%		s
a	Clavel	48%	62%			s
b	Roila		72%	86%	81%	ns
	Pater*			41%	47%	ns
	Sorbe			72%	76%	Ns
[2] Highly Emetogenic						
a	Olver*	49%	54%			s
a	Gandaria*	33%	40%			s
a	Navari*	37%	56%			s
b	Dreschler		53%		80%	s
b	Garcia del Muro		39%		60%	s
c	Johnston			35%	38%	ns
c	Latreille*			33%	36%	ns
c	Italian Group*			60%	62%	ns

*Same anti-emetic Rx on day 1 [as vomit d1 → vomit d2 + on]
s = significant ns = non-significant

Summary:

- **Anti -5HT3 or Corticosteroid is a little better than nothing; use either alone; corticosteroid more cost effective**
- **See Aprepitant and Palonosetron Appendices**

APPENDIX 14

ANTIEMETIC EFFICACY OVER REPEATED CYCLES

	Cycle			
	1	***3***	***6***	***[Day 1 Results]***
[1] Moderately				
Soukop	95%		65%	
Kaizer	81%	84%		
Roila	92%	90%		
[2] Highly				
Ritter	42%	38%		
Dewitt	66%	40%	31%	
Gridelli	63%	64%		

- Complete control rate falls as # of cycles passes 3
- Similar results for delayed phase
- Given drop out of failures 'CR' rate should increase over repeated cycles if efficacy maintained.

APPENDIX 15a

NK1 INHIBITORS. HIGHLY EMETOGENIC

1. NK1 receptors less good than 5HT3 on day 1

Campos	2001	NK1/Dex vs Gran/Dex	46% vs 57%	^{0} emesis
Cocquyt	2001	NK1 vs Ond	37% vs 52%	
Vanbelle	1996	NK1 vs Ond	37% vs 48%	

2. Triple therapy day 1 superior

			d1 ^{0} emesis
Campos	2001	Gran/Dex/NK1 vs Gran/Dex	80% vs 57%
Hesketh	2003	Ond/Dex/NK1 vs Ond/Dex	89% vs 78%

3. NK1 provides superior control in delayed phase

* DeWit 2003

d1	d2-5	^{0} emesis d1-5
Ond/Dex/NK1	Dex/NK1	64%
Ond/Dex	Dex	49%

* Hesketh 2003

d1	d2-4	^{0} emesis d1-5
Ond/Dex/NK1	Dex/NK1	73%
Ond/Dex	Dex	52%

* Poli-Bigelli 2003

d1	d2+3	CR d1-5
Ond/Dex/NK1	Dex/NK1	63%
Ond/Dex	Dex	43%

* (Aprepitant 125 mg po d1, 80 mg po od d2+3: dose identified from study by Chawla 2003)

NB: (1) Aprepitant still superior even if no emesis on day 1 (83% vs 67% d1-5 control rate)
(2) Original Hesketh study, day 1 NK1 all that was needed but dose Aprepitant was 400 mg not 125 mg.

APPENDIX 15b

Aprepitant and moderately emetogenic

Essentially Breast Cancer "AC" type, except Rapoport study

			(A)	(B)
(1)	Yeo		Aprep 125 → 80 d2+3 po Ond 8 mg x 2 po d1 Dex 12 mg po d1	Ond 8 mg bid d1→3 Dex 20 mg po
	^{0} vomit→	0-120 hrs	55%	50%
	^{0} nausea →	0-120 hrs	31%	36%
	CR →	0-120 hrs	47%	42%
(2)	Warr		Aprep 125, 80, 80 d1-3 Ondans 8 po q8 x 2 po Dex 12 po	Ond 8 mg q8 x 2d1, then q12h x4 po Dex 20 mg po d1 po
	CR 0-24		76%	69%
	CR 0-120		51%	42%
	^{0} vomit 0-120		76%	59%
(3)	Rapoport (All MEC types)		Aprep 125, 80, 80 d1-3 Ond 8 mg q8 x2 Dex 12 mg po x1	Ondans 8 mg po q8 x 2 then q12h x4 Dex 20 mg po pre chemo
	<u>Non AC</u>:	d1	93% (96)	88% (92)
		d2-5	76% (84)	69% (74)
	<u>AC</u>:	d1	84% (87)	73% ((76)
		d2-5	65% (70)	53% (60)

( ) = no vomit rates; otherwise are CR rates

- <u>Hence</u> Breast: +/- use aprepitant routinely
  Non-breast: use if prior cycle failure

APPENDIX 16

FUTURE DIRECTIONS

[1] PURE DOPAMINE D_2 ANTAGONISTS

Metopimazine = phenothiazine derivative; related to prochlorperazine

Herrstedt		*Anti-5HT3*	*Anti-5HT3/Metopimazine*
FEC	dl	47%	63%
	d2-5	50%	73%
Cisplatin	d1	50%	78%
	d2-5	31%	52%

⟹ Metopimazine adds to efficacy of 5HT3:
but does it add over and above a steroid?

Lebeau		*Anti-5HT3/Steroid*	*Anti-5HT3/Metopim/Steroid*
Cisplatin	d1	75%	87% p=0.007
	d2-3	39%	53%

⟹ Additional activity over anti-5HT3/steroid combination

[2] Coculine (complex homeopathic medicine in France)

Breast cancer "AC" based, std antiemetic = 5HT3 antag + prednisolone

Cycle 1

	#	Any vomiting	Any nausea	No Q of L↓
Standard	217	41	164	103
Standard + Cocculine	214	35	155	102

Perol 2012

[3] Gabapentin

			d1		d1-5	
	#		^{0}Emesis	^{0}Nausea	^{0}Emesis	^{0}Nausea
1. Ond/Dex d1	Dex d2+3	40	35	29	30	21
2. Ond/Dex d1	Dex d2+3	40	38	28	36	29
	+ Gabapentin d5-d1					

p0.06

Melo Cruz 2012

Phase III North Central Cancer Treatment Group – pending results

APPENDIX 17

Single dose NK1 receptor inhibitor

(No vomit rates d1-5)

1. Casopitant (Grunberg 2007)

	HEC	"AC" BREAST
Control	68%	63%
3 Day*	83%	78%/81%
1 Day [150 mg po]	86%	80%

* 90 mg IV d1, 50 mg po d1+2 or 150 mg po d1, 50 mg po d2+3

2a. Aprepitant (Herrington 2008) HEC + "AC"

	#	
3 Day (125 mg po 80 mg D2+3)	29	93%
1 Day (125 mg po)	30	93%

ie Single day 1 dose as good as 3 day

Control arms "standard" 5HT3 + dexamethasone

HEC

	#	CR d1-5	
2b. A. 5HT3/DEX/Aprepitant po d1-3	1175	72%	(Grunberg 2011)
B. 5HT3/DEX/d1Fosaprepitant 150 mg IV	1147	72%	

3a. HEC=cisplatin chemo N=single day neputitant with palonosetron as combined pill

		CR 0-120	CR 0-24	CR 24-120
N100 + Palonestron 0.5 mg po	dl + dex dl -4	87%	93%	90%
N200 + Palonestron 0.5 mg po	dl + dex dl -4	88%	93%	91%
N300 + Palonestron 0.5 mg po	dl + dex dl -4	90%	98%	90%
Aprepitant dl -3 + ondansetron	dl + dex dl -4	87%	95%	89%

i.e. NETUP/PALO ≡ APREP/ONDANS Hesketh Ann Oncol 2014

3b. MEC (75%), HEC (24%) Gralla Ann Oncol 2014

	CR 0-120
Dex + [N300 + P 0.5]* dl	81%
Dex + PALON 0.5 dl + APREP dl-3	76%

nb If HEC had dex dl-4

*SINGLE PILL NETUPITANT + PALONOSETRON

i.e. NETUPITANT ≡ APREPITANT

APPENDIX 18

Multiday Cisplatin in Germ Cell Tumors Albany

Cross over study design

5HT3 (d1-5) + Dex (d1-2, d6-8) ± Aprep d3 (125 mg) + d4-7 (80 mg)

CR Rate

	No Aprep	Aprep
d1-5	15%	47%
d6-8	35%	63%

APPENDIX 19 OLANZAPINE AND HEC

Blocks multiple neurotransmitters
Dose 5-10 mg po daily
Minor sedation is likeliest S/E
Studies in HEC (cisplatin ≥ 70 or breast cancer)

		DAY 1	DAY 2-5	DAY 1-5	
NAVARI 2011					
(P+D ± O)	Nausea^{O}	87%	69%	69%	Olanzapine√
10 mg po od		87%	38%	38%	Olanzapine^{O}
n=241					
	Vomiting^{O}	97%	77%		Olanzapine√
		87%	73%		Olanzapine^{O}
NAVARI 2016	Nausea^{O}	74%	42%	37%	Olanzapine√
N=380		45%	25%	22%	Olanzapine^{O}
(5HT3+Dex+NK1±0)					
	Vomiting^{O}	86%	67%	64%	Olanzapine√
		65%	52%	41%	Olanzapine^{O}
TAN 2009	Nausea^{O}	95%	70%	70%	Olanzapine√
N=229		91%	30%	28%	Olanzapine^{O}
(5HT3+Dex ±O)					

P: Palonosetron
D: Dexamethasone
5HT3: Palonosetron or ondansetron
NK1: Aprepitant or Fosaprepitant
O: Olanzapine

APPENDIX 20

SEROTONIN SYNDROME

Health alerts, product labeling by FDA, Health Canada etc.

(1) Hypothesis:

↑ serotonin due to drugs + 5HT3 antag → overstimulation (5HT1 and 2)

(2) MAY NOT BE REAL:

1) Case reports only
2) No convincing data that 5HT3 antag per se can ↑ [serotonin] 10-50 x that is needed (in setting of serotonergic drugs)

(3) However as a precaution use 1) 5HT3 antagonists whenever possible as pre-chemo only, 2) avoid if possible unnecessary medical serotonergic drugs and. St. John's Wort, cocaine, ecstacy,tryptophan.

Clinical diagnosis (Hunter Criteria), no diagnostic tests

(4)

MILD	MODERATE	SEVERE
nausea	hyperreflexia	clonus ++
diarrhea	diaphoresis	rigidity
insomnia	T ↑ < 39	T > 39
tremor	agitation	death
anxiety	dysphoria	
	clonus +/-	
resolves 1-3 days	admit	as moderate
	+ hydrate	+ cyproheptadine
	± sedate	± chlorpromazine
	control temp	± benzodiazepine

(5) Serotonergic drugs

- SRI's, MAOI's
- St. John's Wort, Tryptophan
- Cocaine, ecstasy
- Tramadol, fentanyl, pentazocine, lithium, meperidine

FOR USEFUL REVIEW OF MANAGEMENT see" UP TO DATE"

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