Chemotherapy induced emesis: Are we doing are best?

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Conflict of interest

- Merck: speakers bureau and consultant
- Eisai: consultant

Outline

- What is “the best” (are the major guidelines actually the best possible approach?)
- How often do we follow guidelines?
- Why don’t we follow guidelines?
- What is underway at Cancer Care Ontario?

ASCO, MASCC/ESMO and NCCN

- All make virtually the same recommendation for the more emetogenic chemotherapy (a ‘setron + dexamethasone + aprepitant)
- MASCC/ESMO doesn’t recommend dexamethasone beyond day1 for “AC” type chemotherapy
- Based upon many double blind randomized trials with the three major antiemetic classes (corticosteroids, 5-HT_3 RA, NK_1 RA)


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MASCC/ESMO Antiemetic Guidelines 2010

Committee I (2/5): Emetic Risk Groups – Single IV Agents

HIGH **>90%**	Cisplatin Mechlorethamine Streptozocin Cyclophosphamide ≥ 1500 mg/m2 Carmustine Dacarbazine	
MODERATE **30-90%**	Oxaliplatin Cytarabine > 1000 mg/m2 Carboplatin Ifosfamide Cyclophosphamide < 1500 mg/m2 Azacitidine Alemtuzumab	Doxorubicin Daunorubicin Epirubicin Idarubicin Irinotecan Bendamustine Clofarabine

MASCC/ESMO Antiemetic Guidelines 2010

Committee I (3/5): Emetic Risk Groups – Single IV Agents

LOW 10-30%	Paclitaxel	Mitomycin
	Docetaxel	Gemcitabine
	Mitoxantrone	Cytarabine ≤ 1000 mg/m2
	Topotecan	5-Fluorouracil
	Etoposide	Bortezomib
	Pemetrexed	Cetuximab
	Methotrexate	Trastuzumab
	Doxorubicin HCL liposome injection	Catumaxomab
	Temsirolimus	Panitumumab
	Ixabepilone	

SUMMARY ACUTE NAUSEA AND VOMITING

EMETIC RISK GROUP	ANTIEMETICS
High	5HT3 + DEX + APR
Anthracycline + Cyclophosphamide (AC)	5HT3 + DEX + APR
Moderate (other than AC)	PALO + DEX
Low	DEX
Minimal	No routine prophylaxis

5HT3 = serotonin receptor antagonist | DEX = DEXAMETHASONE | APR= APREPITANT | PALO = PALONOSETRON

SUMMARY DELAYED NAUSEA AND VOMITING

EMETIC RISK GROUP	ANTIEMETICS
High	DEX + APR
Anthracycline + Cyclophosphamide (AC)	APR
Moderate (other than AC)	DEX
Low	No routine prophylaxis
Minimal	No routine prophylaxis

DEX = DEXAMETHASONE

APR= APREPITANT

Would I follow all of the recommendations?

- No
- Dexamethasone beyond 24 hours for all MEC (published evidence doesn't support it)
- Aprepitant for "highly emetogenic" category other than cisplatin (+AC chemo for breast cancer)
  - DTIC in ABVD treated with palonosetron
  - CHOP (a type of AC) treated with palonosetron
- Including 'mibs or 'mabs in a classification system of chemotherapy emetogenicity (zero evidence to suggest same treatment is appropriate)

Are the guidelines otherwise correct?

- That said, its hard to ignore the multiple double blind RCTs that support :

1) Triple therapy for “AC” in breast cancer or cisplatin ≥70 mg/2 for control of vomiting or retching and patient function

2) Palonosetron as a preferred ‘setron at least in the absence of aprepitant Likun Oncologist 2012 OR 0.64, $p<0.0001$

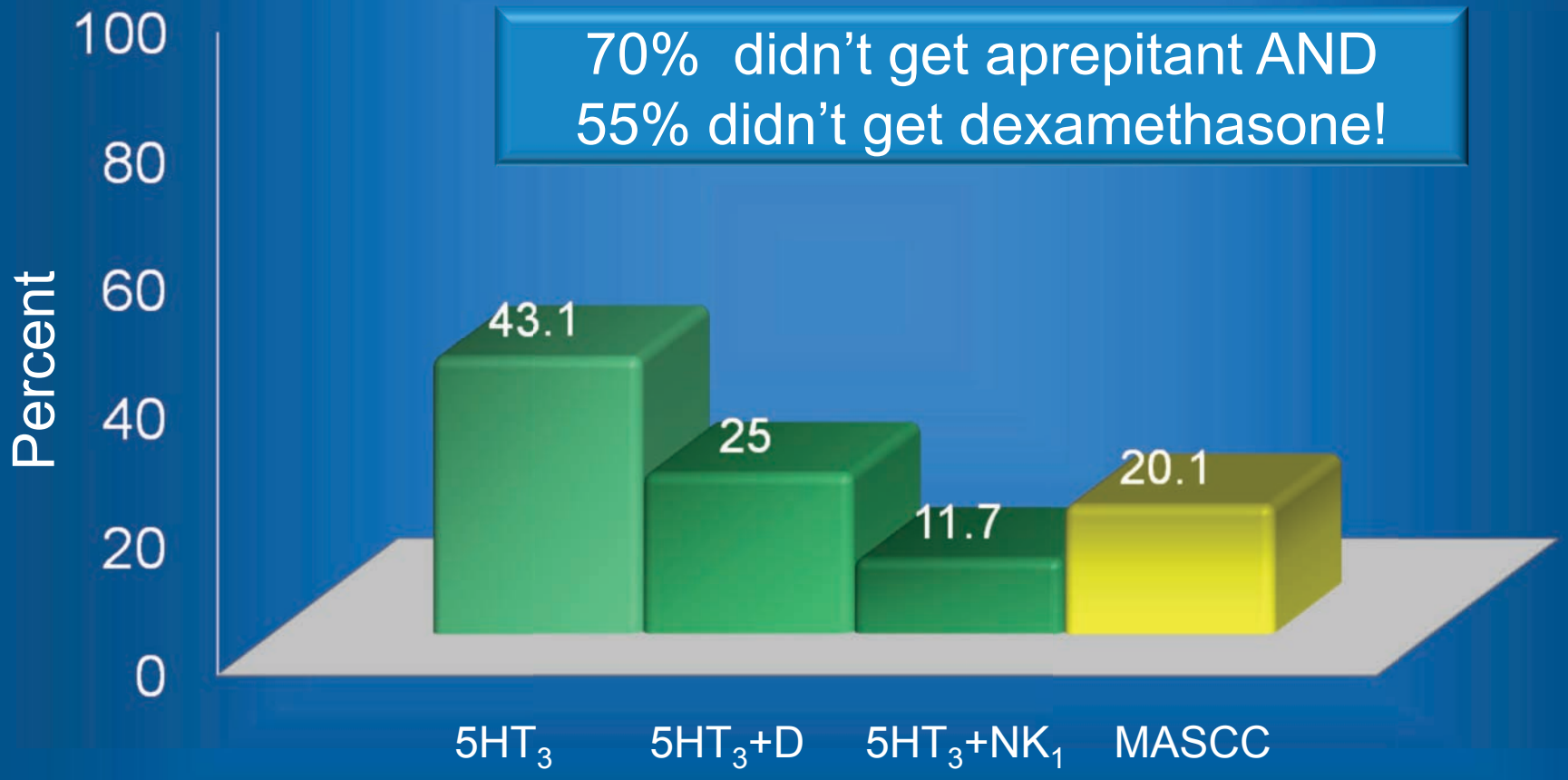
How often do we follow the antiemetic guidelines?

Antiemetic use versus Admissions

Hatoum Support Care Cancer 2012

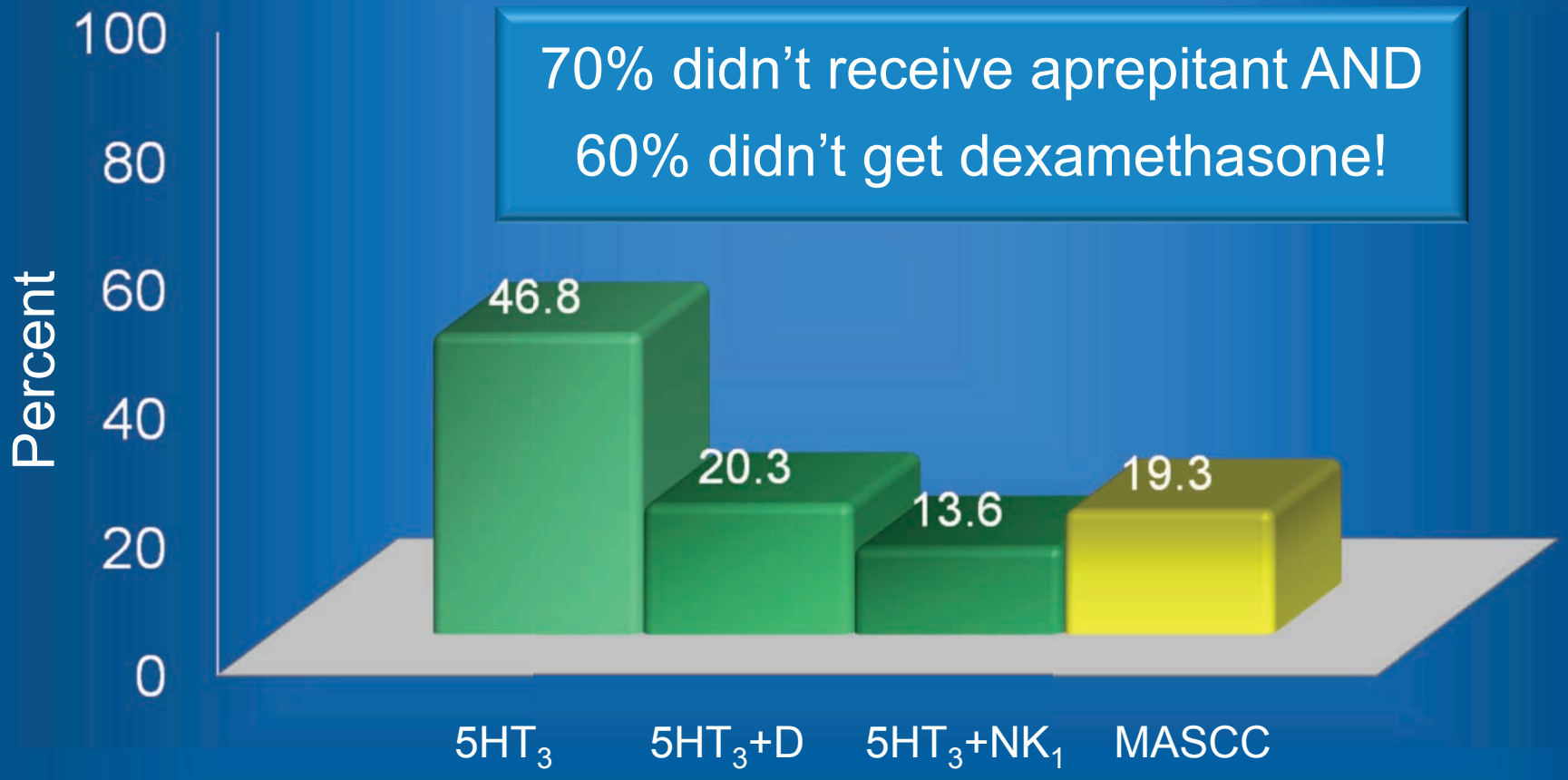
- Used Pharmetrics database for 2005-2008 (USA, covers ~ 100 payer plans)
- Disease/procedure billing codes for nausea, vomiting or dehydration
- Their intent was to show that palonosetron was a superior 5-HT_3 RA
- I have combined the 5-HT_3 RA data and looked at how often the three drug classes were used

Antiemetic use for AC (breast cancer) N=4868



Based upon Hatoum Support Care Cancer 2012;20(5):941-9

Antiemetic use for Cisplatin (lung cancer) N=1692

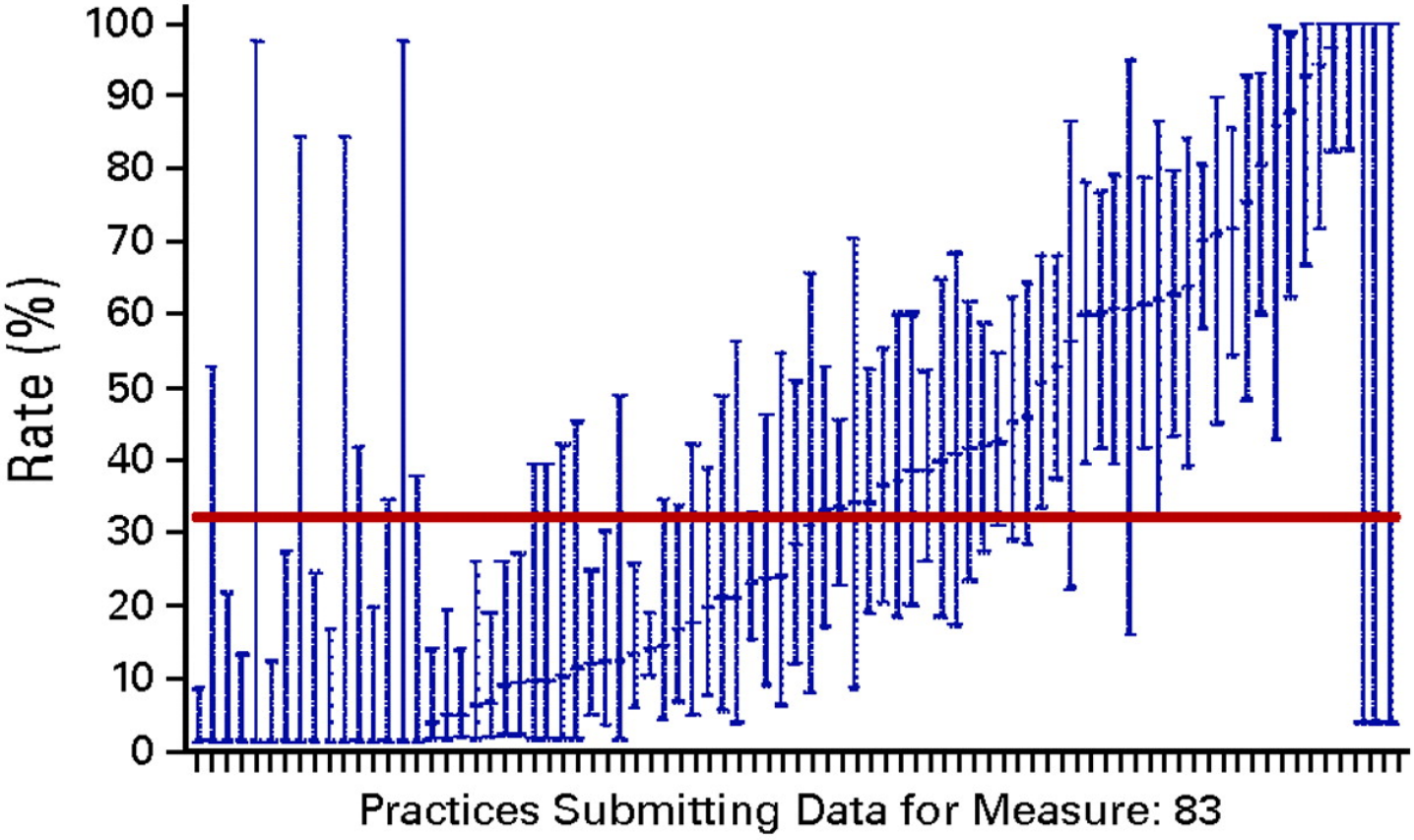


Based upon Hatoum Support Care Cancer 2012;20(5):941-9

Did it matter in the end?

- Breast cancer admissions: 5.2%
- Lung cancer admissions: 21.2%

Heterogeneity in aprepitant use: QOPI data from 2006 (HEC)



http://jop.ascopubs.org/cgi/reprint/3/5/271

Informal PMH e-survey

- Asked 12 oncologists in the breast, lung and ENT group about their prescribing habits for aprepitant in chemotherapy for which it is recommended ("AC" and high dose cisplatin)
- One: no response
- Five: "always"
- Two: only if private insurance
- Three: no (might if problems with cycle 1)

Guidelines versus practice

- Did not survey corticosteroid or ‘setron use because its automatically incorporated into OPIS
- I have not heard of dexamethasone fears in talks in Canada
- Will focus on why are most medical oncologists don’t prescribe aprepitant according to guidelines

Courtesy of Arnie Aberman

- A man was being sued for returning a borrowed lawn mower in a damaged condition.
  His lawyer told the court:
- Firstly, he never borrowed the lawn mower.
- Secondly, if he did borrow it, the lawn mower was in perfect condition when he returned it. “
- Thirdly, if it was broken, the lawn mower was already damaged when he borrowed it.
- (A moving target of explanations)

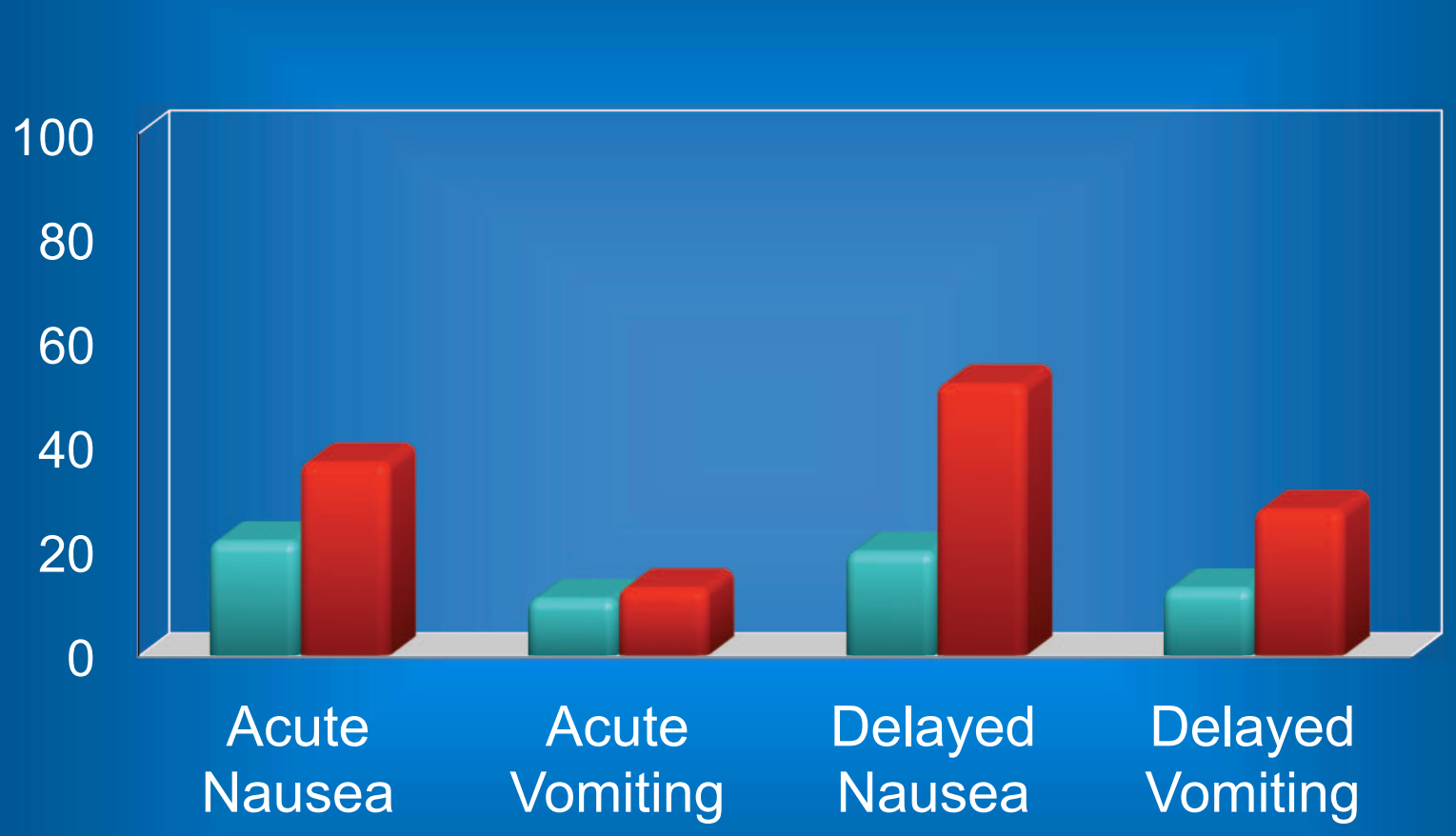
Potential Issues

- Vomiting is not that common anymore
- If it is more common than I think, its not that bad
- If it is that bad, aprepitant doesn't add much
- If it does add a lot, there are drug interactions and side effects
- Even if there are no interactions or no side effects, my patients can't afford it
- Even if most patients can get it without cost, it takes time and effort to order

Perception of frequency: Anchor study

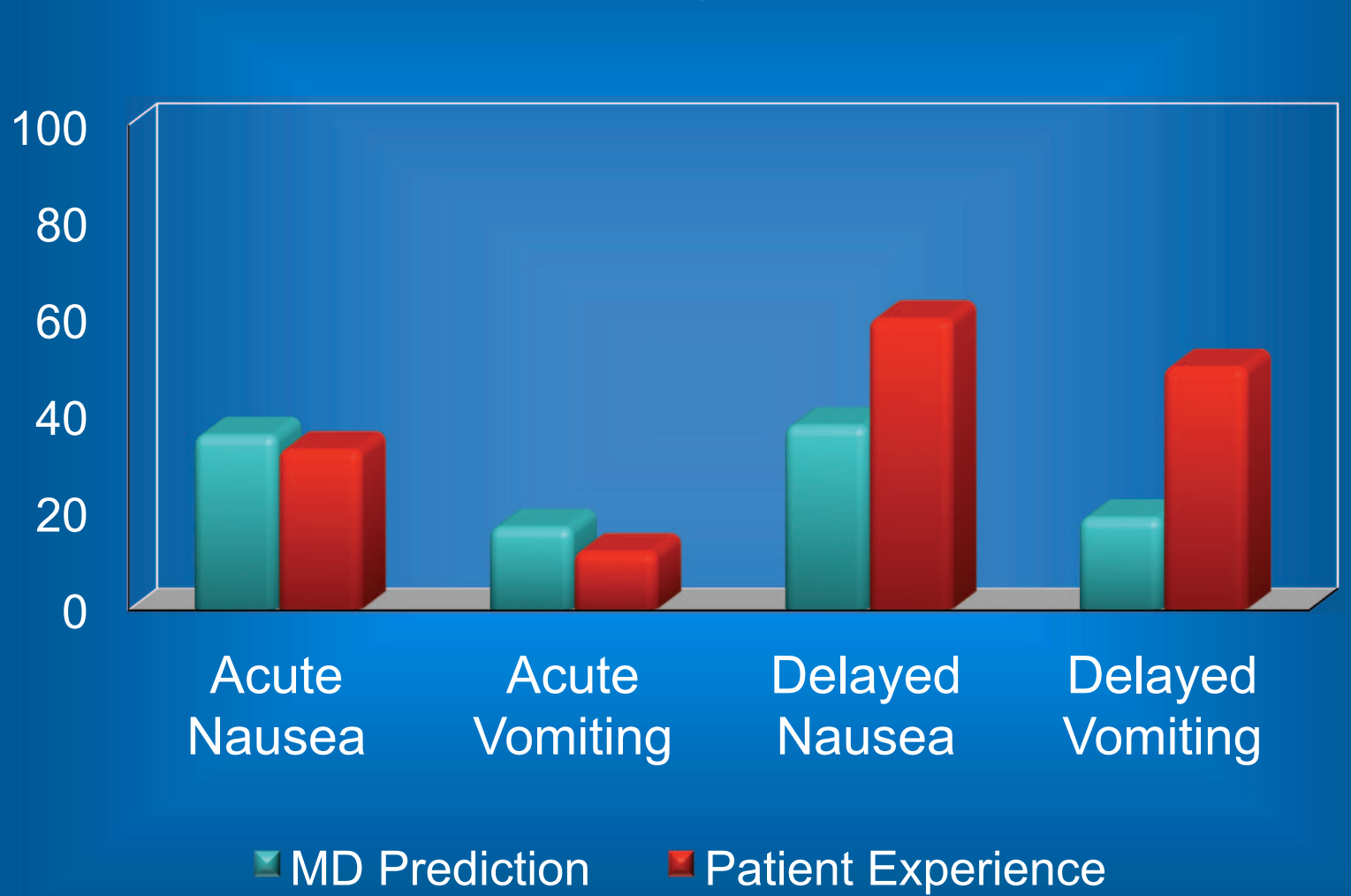
- Survey of 8 oncologists from different countries around the world and patients from their clinics receiving cisplatin or moderately emetogenic chemotherapy (no aprepitant)
- Oncologists and nurses predicted the likelihood of emesis
- Consistently underestimated the likelihood of nausea and vomiting beyond 24 hours

Perception vs Reality: MEC (n=231)



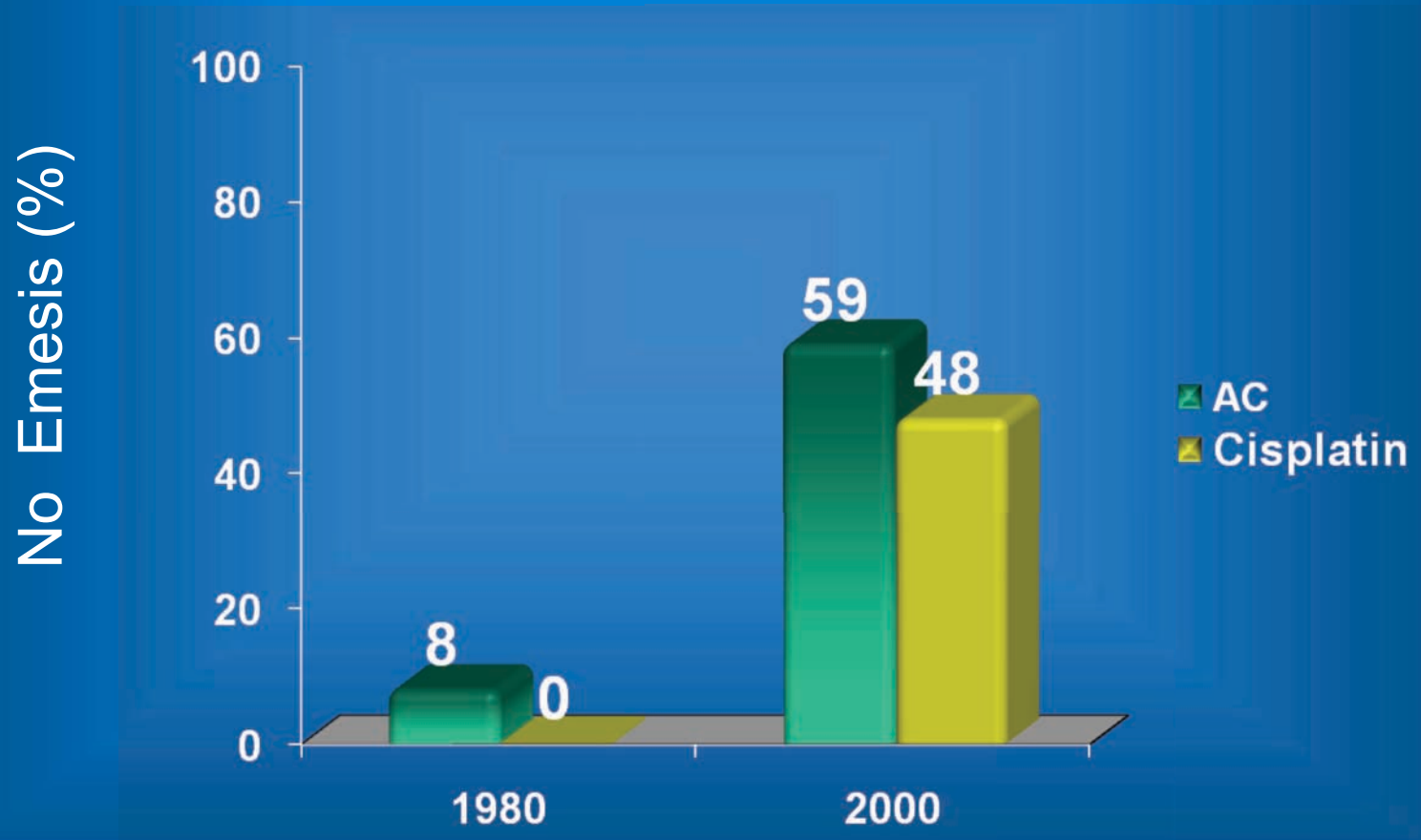
From ANCHOR study Grunberg Cancer 2004

Perception vs Reality: Cisplatin (n=67)



From ANCHOR study Grunberg Cancer 2004

A 5-HT_3 RA+ Dexamethasone Provided A Huge Advantage Over Rx From 1980



Palmer BMJ 1980; Gralla NEJM 1981; Warr J Clin Oncol 2005; Warr Eur J Cancer 2005

Is A ‘Setron + Corticosteroid Sufficient?

- > 30% rate of emesis should be unacceptable
- Results diminish over several cycles, at least with a 5-HT_3 RA and corticosteroid de Wit Eur J Cancer 2004, Herrstedt Cancer 2005

What we've had since 1991 is good enough (or at least its not "that bad" – grade 3 vomiting is rare)

CTCAE 4.0 – If its not Gr 3, isn't it "well tolerated"?

	Gr 1	Gr 2	Gr 3	Gr 4
Nausea	Loss of appetite, eating normally	Oral intake ☐ without eating habit change	Oral intake ☐ without dehydration or	IV fluids, feedings or TPN ≥ 24 hrs
Vomiting	1 episode in 24 hrs	2-5 episodes in 24 hrs	> 6 episodes in 24 hrs, IV fluids or TPN > 24 hrs	Life threatening

If you think that grade 2 is just fine, I want another oncologist!

Does a “little” vomiting really matter?

- 60 year old woman with NSCLC
- About to receive cycle #1 of cisplatin 70 mg/m^2
- S[illegible]only o[illegible]

Does that last point sound as bad to YOU as it does to me?

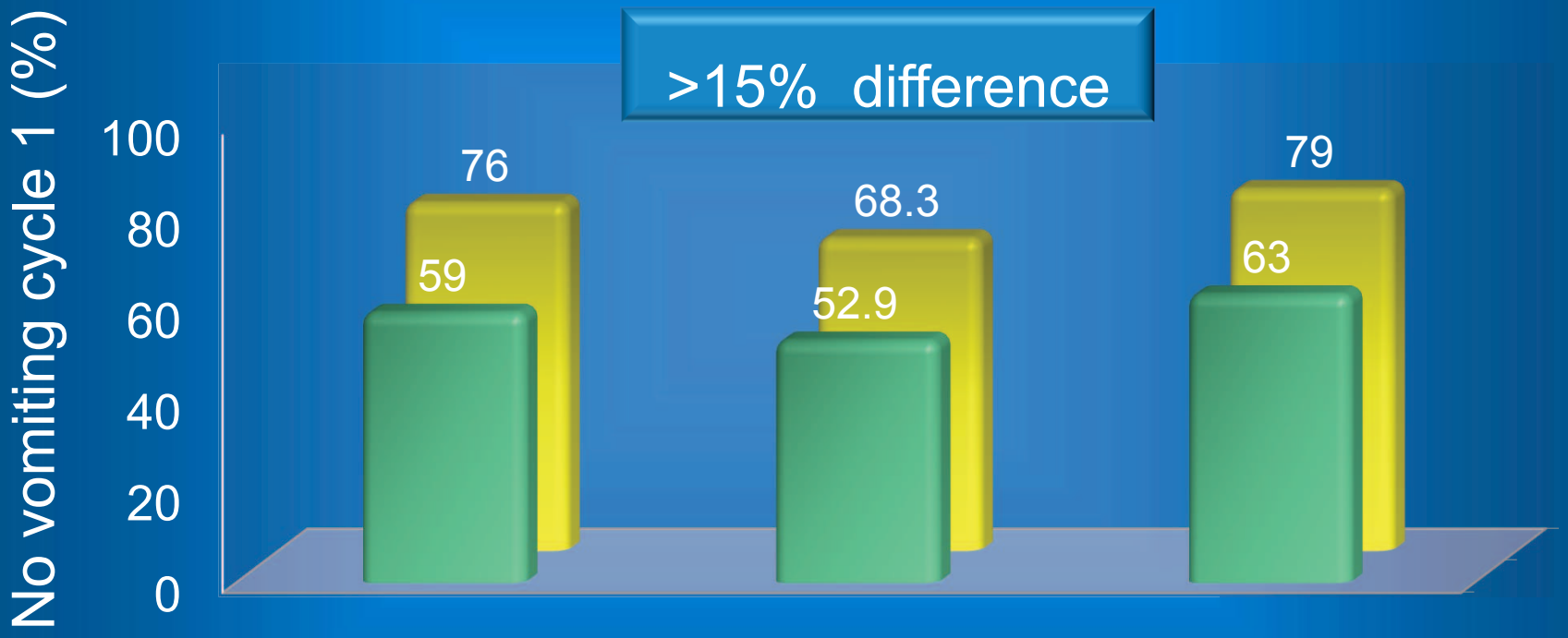
- She vomits a couple of times and misses Seder/ Good Friday family dinner because she couldn’t sit down at the table
- What’s the big deal? It isn’t her first holiday dinner and it may (or may not) be her last.

Is the incremental benefit not large enough with an NK_1 RA?

- Meta-analyses on absolute number of patients with emesis prevented:
- $5\text{-}HT_3$ RA: 11-17% Jantunen Eur J Cancer 1997
- Dexamethasone: 16% Ioannidis J Clin Oncol 2000
- How large is the incremental benefit with an NK_1 RA?

Phase III trials with AC

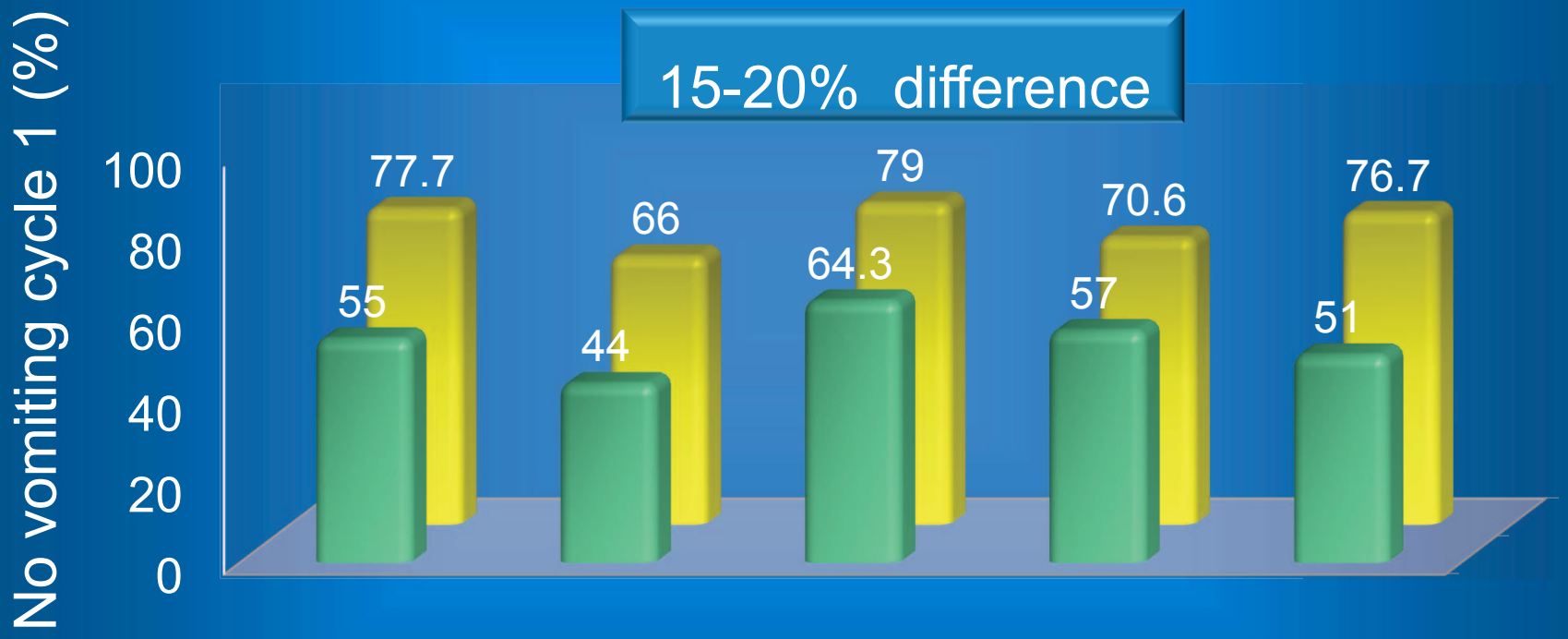
(5-HT_3 RA day1-3 plus dexamethasone day 1)



Warr J Clin Oncol 2005, Rapoport Support Care Cancer 2010, Herrstedt J Clin Oncol 2009 (casopitant)

Phase III trials with cisplatin > 70 mg/m2

(5-HT_3 RA day1 plus dexamethasone day 1-4)



Hesketh J Clin Oncol 2003, Poli Bigelli Cancer 2003, Schmoll Ann Oncol 2006, Zhang WLC 2011, Takahashi Cancer Sci 2010

What does that tell us?

- The absolute number of patients with emesis prevented by adding an NK_1 RA is similar to that improvement seen with ‘setrons or dexamethasone
- What you don’t see in the trials numbers is that those who vomit in the first 24 hours STILL do better beyond 24 hours if they are on aprepitant Warr Eur J Cancer 2005
- Counted as a “failure” for trial purposes but a gross reduction in vomiting may still be a success from a patient perspective

Safe? Well tolerated?

- Aprepitant is a moderate CYP3A4 inhibitor
- CYP3A4 metabolizes taxanes, etoposide, vinca alkaloids, cyclophosphamide
- CCO HCP information warns that it may interfere with the metabolism of etoposide and paclitaxel potentially requiring a dose reduction

39A□D□I8E9A□90E9□C□3□0□□7A□□□
2□E□G5□2□5□911□□□5C□3C89□□

Concomitant	Aripiprazole N	Aripiprazole □30	Placebo N	Placebo □30
0C□□□89	□□	□(□	□	□(□
4 □□A96□9	□9	□(□	□	□□□(
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% with serious events		15.5%		13.8%

http://www.fda.gov/ohrms/dockets/ac/03/briefing/3928B1_02_FDA-Emend%20Briefing%20Pkg.htm

Additional data

- “AC” study (N=866) showed identical rate of febrile neutropenia in both arms (2.1%) and nearly identical rate of SAEs Warr J Clin Oncol 2005
- PK studies with vinorelbine and docetaxel show NO difference Loos Cancer Chemother Pharmacol 2007;Nygren Cancer Chemother Pharmacol 2005
- PK studies with cyclophosphamide show no difference Walko Cancer Chemother Pharmacol 2005, Bubalo J Clin Pharmacol 2012

Additional data

- No interactions have been reported with IV chemo and other CYP3A4 inhibitors (fluconazole, diltiazem, verapamil, erythromycin)
- If PK studies show no interaction and large RCTs show no difference in toxicity, THERE IS NO INTERACTION!

Patient info not consistent with reality (BCCA)

SIDE EFFECTS
Constipation or **diarrhea** may occur.
Headache may sometimes occur.

http://www.bccancer.bc.ca/NR/rdonlyres/8E2601E7-CE5A-4DE1-9299-0C3C4E76B469/43150/aprepitant_handout_01dec09.pdf

Patient info not consistent with reality (CCO version)

Most Common Side Effects

Tiredness
- Rest often; take naps if needed. Move slowly when getting up.
- Eat well-balanced meals and drink plenty of fluids. Light exercise may help.
- Do not drive a motor vehicle or operate machinery when feeling tired.

Hiccups
- Drink clear fluids and avoid large meals.

Diarrhea
- Drink plenty of clear fluids. Limit hot, spicy, fried foods, foods/drinks with caffeine, orange or prune juice.
- Try a low-fiber BRAT diet (Bananas, white Rice, Apple sauce, Toast made with white bread).
- Take anti-diarrhea drug(s) if given to you by your doctor.
- Also see Diarrhea pamphlet.*

Poor Appetite; don't feel like eating; weight loss
- Eat foods that you like and try to eat regular small meals.
- Use meal supplements if possible. See a dietitian.

Dizziness, lightheadedness
- Do not drive a motor vehicle or operate machinery if dizzy.
- Try to get up and move slowly.

Proteins in Urine
- Look for darkening of urine, body swelling or recent unusual weight gain.

Abnormal liver lab tests
- Your doctor may monitor these regularly. Call your doctor if you have yellowish skin or eyes, or unusual dark urine.

Constipation
- Eat a balanced diet with fibres such whole grains, fruit and raw vegetables.
- Drink plenty of fluids. Try light exercise regularly.
- Speak to your doctor if no bowel movement for 3 or more days.
- Also see Constipation Pamphlet.*

Less Common Side Effects, but may be Severe

Fever, chills, infection
- Phone your doctor right away or go to the nearest emergency department, if your oral temperature is over 38°C or 100.4°F (unless stated otherwise by your healthcare team). Tell the health care team that you are on chemotherapy.
- Check your temperature, especially if you are feeling unwell with sweats, fever or chills.
- Wash your hands often. Avoid sick people and crowds.
- Check with your doctor before getting any vaccines.
- Also see Low White Blood Cells pamphlet.*

Heart problems
(irregular heartbeat, chest pain, fainting, swelling, shortness of breath)

Blood clot (limb pain or swelling, hardened vein in limb), may occur in lungs (sudden start of coughing, breathing problems, chest pain, coughing blood)

Serious skin rash
(may include blisters or skin peeling)

Allergic reaction (fever, severe rash, itchiness, shortness of breath, swollen face, lip or tongue, chest or throat tightness)
- may occur during or shortly after the drug is given.

Seizures, feeling confused

Lung problems
(increased cough, breathing problems, chest pain, coughing blood)

Other less common side effects have been reported:
- heartburn; stomach upset; pain in the belly; headache; mild joint

https://www.cancercare.on.ca/cms/One.aspx?portalId=1377&pageId=11752

Financial barriers: Perceived or real?

- Aprepitant costs ~ $100/cycle
- ~60% of our patients have private insurance
- For seniors, Ontario Works, etc the MOH will fund aprepitant if cisplatin $\geq$ 70 mg/m^2
- Compassionate program by Merck for those in financial need
- Cost has not been a major barrier in Toronto
- (when ‘setrons were expensive and demonstrated not to be beneficial beyond 24 hours it was still common to prescribe x 3-4 days)

Provincial Coverage of Aprepitant

	Cisplatin	2nd line	AC	2nd line
BC	✓		✓	
AB	✓			
SK		✓		✓
MB	✓			
ON	✓			✓
QU	✓			
NB		✓		
NS	✓			
NL	✓			

An “extra effort” barrier

- If you order via OPIS, the ‘setron and dexamethasone are automatic.
- Aprepitant may not be included and it IS awkward to order electronically.
- And do you reduce the dexamethasone?
- At PMH, the breast group (with some arm twisting) was able to get a version of “AC” and gem/cis with and without aprepitant.
- Also exists for the lung, GU and lymphoma group though not everyone knows about it.

An “extra effort” barrier

- OPIS ordering now takes no more effort for those site groups
- The extra effort is for those without private health insurance
- At some cancer centres, this is where the medication reimbursement specialist comes in. This saves me time every week. She knows that for FEC-D, I am interested in both aprepitant and either filgrastim or pegfilgrastim and she checks out the resources

How can we do better?

- Make it easy to order through OPIS or paper options with two options (with and without)
- If a medication reimbursement specialist is present at your centre, work with her/him to establish a workable setup
- Have treatment practices in line with the best evidence, not what government policy is for payment (your allegiance is to the patient, not the government).

Activity at Cancer Care Ontario

- Starting a review of ASCO guidelines to decide what antiemetic recommendations should be made
- Will deal with palonosetron at a later date
- Objective : create antiemetic regimens that can be exported along with the chemotherapy regimens in OPIS (each centre should not have to create the antiemetic regimens from scratch)

Summary

- The key MASCC (and ASCO/NCCN) recommendations are in accord with the evidence from randomized trials
- Prescription of optimal antiemetics for cisplatin and AC chemotherapy is the exception rather than the rule
- The discrepancies are unlikely to be explained by purely economic factors

Summary

- There are barriers in the system that may be addressed (order entry system, access to free drug)
- Anecdotal comments suggest that attitude towards of acceptability of emesis is a factor
- We should treat our patients as we would wish to be treated