Antiemetics: Guidelines, Interactions and more….

Jude Lees
Royal Adelaide Hospital
Adelaide
South Australia

Chemotherapy-induced side effects - the patient's view

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>RANK</th>
<th>Side Effect</th>
<th>RANK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>Loss of Hair</td>
<td>2</td>
</tr>
<tr>
<td>Loss of hair</td>
<td>3</td>
<td>Vomiting</td>
<td>3</td>
</tr>
</tbody>
</table>

Complications of Uncontrolled Vomiting

MEDICAL VIEW
- dehydration
- weight loss
- malnutrition
- electrolyte imbalance
- Mallory Weiss tears (oesophagus)
- dental erosion

PATIENT VIEW
- malaise
- impaired quality of life
- compromised compliance with chemotherapy
- ANTICIPATORY emesis
  - a manifestation of classical conditioning
  - incidence up to 1/3rd patients

Pathogenesis of chemotherapy induced emesis

Substance P
- A neuropeptide of the tachykinin family
- biological activity via the NK 1 receptor

Evidence for involvement in emesis
- substance P identified in
  - afferents from GIT
  - known vomiting areas in the brain
- exogenous substance P causes emesis (animals)
- preclinically - NK1 receptor antagonists displace substance P from NK1 receptors
### Variables Affecting Emetic Outcome

#### Chemotherapy Variables:
- **The drug used**
  - Cytotoxics vary in incidence, time to onset & duration of emesis
  - *e.g.*
    - Incidence:
      - Bleomycin = 10% to cisplatin > 90%
    - Time to onset:
      - Doxorubicin 2 to 6 hours,
      - Cyclophosphamide 6 to 18 hours
    - Duration:
      - Cisplatin > 24 hours
      - Bolus 5FU 3 to 6 hours

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### Variables Affecting Emetic Outcome

#### Chemotherapy Variables:
- **The drug used**
  - Cytotoxics vary in incidence, time to onset & duration of emesis
- **The dose given**
  - High dose cytarabine - highly emetogenic
  - Low dose - low incidence
- **The schedule**
  - Bolus 5FU - moderately emetogenic
  - Continuous infusion - low incidence

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### Variables Affecting Emetic Outcome

#### Patient Variables
- **Age**
  - Older patients have less emesis
- **Gender**
  - Males have less emesis than females
- **Patients with history chronic heavy alcohol intake**
  - Have less emesis
- **Prior emetic history**
  - Vomiting in previous cycles predicts poor response; possible relationship to prior motion sickness & morning sickness
- **Anxiety**

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### Goals of Antiemetic Treatment
- Prevent nausea & vomiting, rather than treat established emesis
- Achieve control in acute & delayed settings
- No added side effects
- Easy to use
- Cost effective!!
**Current Antiemetics Chemotherapy**
- 5 HT3 receptor antagonists (setrons)
- NK 1 receptor antagonist (aprepitant)
- corticosteroids (dexamethasone)
- dopamine antagonists - metoclopramide, prochlorperazine, domperidone etc.
- anxiolytic/amnesics - eg lorazepam

**How Do We Use Antiemetics in Practice?**
1. Consult & Review Published Guidelines (evidence based) e.g.
   - Multinational Association of Supportive Care in Cancer (2004/5) - www.mascc.org
   - American Society of Clinical Oncology 2006 - www.asco.org

**What Guidelines Provide**
- Group individual cytotoxic agents into categories according to emetic risk
  - High, Moderate, Low (and Minimal)

**MASCC 2004 ANTIEMETIC GUIDELINES**

<table>
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<th>Emetic Risk Groups - Single IV Agents</th>
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<tr>
<td><strong>HIGH</strong></td>
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<tr>
<td><strong>MODERATE</strong></td>
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**What Guidelines Provide**
- Group individual cytotoxic agents into categories according to emetic risk
  - High, Moderate, Low (and Minimal)
- Antiemetics for each emetic risk group in both acute and delayed settings

| LOW | Paclitaxel, Docetaxel, Mitoxantrone, Topotecan, Etoposide, Pemetrexed, Methotrexate, Doxorubicin HCL lipo |
| MINIMAL | Bevacizumab, bleomycin, busulfan, cladribine, fludarabine, vincristine, vinblastine, vinorelbine |
High Emetic Risk
ACUTE setting

MASCC  NCCN  ASCO
5HT3 antagonist  5HT3 antagonist  5HT3 antagonist
+  +  +
dexamethasone  dexamethasone  dexamethasone
+  +  +
aprepitant  aprepitant  aprepitant
+/- lorazepam

See Guidelines in full at websites

How Do We Use Antiemetics in Practice?

2. Implement the Guidelines into your own practice
   - a multi-disciplinary team
   - people who understand the problem
   - strong team leader
   - determine a guideline
   - keep it standard and as simple as possible
   - address all areas including multi-day chemo (no evidence base)

How Do We Use Antiemetics in Practice?

3. Educate all users

4. Evaluate results in your setting

5. Amend as appropriate

6. Ensure you keep up with new developments

Unanswered Questions

- Nausea as main endpoint
- Low risk settings
  - No randomized studies, low level of evidence
- Paediatrics
  - Need to do separate studies not translate from adults
  - MASCC Antiemetic Study Group to address 2006
- Radiation Therapy
- High dose chemotherapy/transplant

Unanswered Questions

- Prospective evaluation of emetic potential of:
  - new chemotherapy agents: oxaliplatin, pemetrexed etc
  - targeted therapies: gefitinib, erlotinib, erbitux etc
- Long-term treatment studies
  - Oral chemotherapy
- Specific methodology in:
  - Multiple cycle studies
  - Multi-day chemotherapy protocols
Interactions Between Antiemetics and Antineoplastic Agents

Aprepitant
• aperpitant metabolism pathways very complex
• is a cytochrome P450 (CYP) 3A4 isoenzyme substrate
• used for >14 days, is a potent inducer of CYP3A4 and 2C9
• used for 3 days/cycle is a moderate inhibitor of CYP3A4

Aprepitant Is a Moderate CYP3A4 Inhibitor
Inhibition of CYP3A4 Ranked According to Fold Increase in Oral Midazolam AUC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Strength</th>
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<tbody>
<tr>
<td>Ketoconazole</td>
<td>Strong</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Strong</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Strong</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Strong</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Moderate</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Moderate</td>
</tr>
<tr>
<td>Grapefruit juice</td>
<td>Strong</td>
</tr>
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</table>

Aprepitant regimen produces CYP3A4 inhibition comparable to grapefruit juice and widely used drugs (e.g., diltiazem, verapamil).

Aprepitant Interactions with Antineoplastic Agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Potential Interactions</th>
</tr>
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Pivotal Studies 052 (USA) & 054 (Latin America)

- Cisplatin+ chemo metabolised by CYP3A4 e.g. cyclophosphamide, etoposide, taxanes & vinca alkaloids
- 052 - no significant difference in toxicity
- 054 - higher incidence of SAE compared in aprepitant arm (15.8% vs 8.5%)
  - most common neutropenia, febrile neutropenia, thrombocytopenia & dehydration

Conclusions

Docetaxel - small crossover trial

- 10 patients
- AUC, maximum plasma conc, clearance & T1/2 similar when given with or without aprepitant
- Mean nadir ANC not significantly different: 960 cells/mm$^3$ with aprepitant vs. 850 cells/mm$^3$ without

Hande K et al. An open-label, balanced, two-period crossover study to investigate the influence of aprepitant on docetaxel pharmacokinetics (abst. 2094, ASCO 2004)

CONCLUSION
Massaro & Lenz

- Docetaxel is a representative agent eliminated via CYP3A4
- data indicate that inhibition of CYP3A4 by aprepitant is:
  - modest
  - may not have a significant impact on chemotherapy-related toxicities

Recommendations
Massaro & Lenz

- No empiric dose adjustment is recommended for concurrent chemotherapy
- monitor patients for signs of increased toxicity with drugs metabolized via CYP3A4

Recommendations
Massaro & Lenz

- Aprepitant has the potential to decrease anti-tumor effects of drugs activated by CYP3A4 (eg cyclophospham, ifosfamide)
- caution routinely using aprepitant with cyclophosphamide, particularly in the setting of stem-cell transplant, until pharmacokinetic data are available

Cyclophosphamide & Thiotepa

- de Jonge et al. evaluated effect of aprepitant on
  - pharmacokinetics & metabolism

Cancer Chemotherapy & Pharmacology (2005) 56: 370-8
Aprepitant inhibits cyclophosphamide bioactivation and thiotepa metabolism.

- High dose chemotherapy regimen
  - cyclophosphamide 1.5g/m2/day D 1 to 4
  - carboplatin AUC 5 D 1 to 4
  - thiotepa 60 mg/m2 12 hourly D 1 to 4
  - mesna
- 6 patients full dose
- 2 patient 2/3 dose
- concurrent meds - ciprofloxacin, fluconazole, ranitidine, Vit K, folic acid

Antiemetics
- granisetron 1mg IV twice daily D 1-6
- dexamethasone 10mg* IV twice daily D 1-4 once daily D 5-6
- aprepitant 125 mg Day 0; 80 mg daily to D 7

* dex. dose NOT reduced for aprepitant

Blood collected on D 1 + 3 analyzed for:
- cyclophosphamide & its activated metabolite 4-hydroxycyclophosphamide
- thiotepa & its main active metabolite tepa
- analyzed using population pharmacokinetic
- reference population 49 pts on same chemo without aprepitant sampled under same conditions

When Aprepitant Co-administered:
- rate of autoinduction of cyclo í 23% (P=0.040)
- formation clearance of tepa í 33% (P<0.001)
- exposure to active metabolite 4-hydroxycyclophosphamide í 5%
- exposure to tepa í 20%

Conclusion de Jonge et al.
- effects of aprepitant interaction with cyclophosphamide & thiotepa are small compared to total variability
- antiemetic control superior
- but who is using it?

Summary
Aprepitant/Cytotoxic Interactions

Potential to either:--
- INCREASE exposure of the cytotoxic
  MONITOR FOR È TOXICITY
or
- DECREASE formation of active drug
  MONITOR FOR ë EFFECT
Off the Beaten Track...
Little-Known Antiemetics.

What Are the Results?

What Other Options for Chemotherapy-Induced N&V?

- Cannabinoids
- Ginger
- Acupressure/acupuncture
- Olanzapine
- Gabapentin

Olanzapine

Chemical Name:
2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3b][1,5] benzodiazepine

- atypical antipsychotic
- activity at multiple dopaminergic D₄, D₃, D₁, D₂, serotonergic 5HT₂A/2C, 5HT₂₅, 5HT₆, muscarinic m₁-m₅, and histaminic H₁ receptor sites
- has 5 X affinity for 5HT2 than D2 receptors
- fewer extrapyramidal side effects
- È potential as antiemetic

Olanzapine

- Observation: psychiatric patients on narcotics had less nausea when taking olanzapine

Olanzapine

Phase II trial Navari et al Supportive Care in Cancer. 13(7):529-34, 2005

30 chemotherapy-naïve patients (>50% had breast cancer)

Antiemetic Protocol

- Day -2, -1 pre chemo: olanzapine 5mg/day
- Day of chemo: 10 mg olanzapine + IV granisetron + dexamethasone
- Days 2-4 post chemo: 10 mg/day olanzapine +dexamethasone 8 mgBD (day 2 & 3) then 4 mg BD on day 4

Olanzapine Results

Acute:

- 100% complete response (no emesis, no rescue) regardless of emetogenicity of chemo

Delayed:

- 10 pts. had highly emetogenic chemo - cisddp70 mg/m² or cisddp + doxorubicin
- 80% had a complete response (vomiting)
- 20 pts had moderately emetogenic chemo (doxo 50 mg/m² or doxo+ cyclo or irinotecan)
- 85% complete response
Olanzapine Results - Nausea

- 10 patients on HEC: no nausea during the acute or delayed period
- 20 patients on MEC: 85% had minimal or no nausea in acute period; 65% during the delayed period
- in subsequent cycles (25 patients, cycle 2 & cycle 3; 21 patients, cycle 4)
  - CR (emesis) and nausea control were equal to or greater than cycle 1

Conclusions Navari et al

Olanzapine:
- safe and highly effective
- controlled acute and delayed chemotherapy-induced nausea & vomiting
- patients received highly & moderately emetogenic chemotherapy

My Conclusion - Olanzapine

- used in 3 patients on highly emetogenic chemotherapy or BMT refractory to standard antiemetics
- very effective
- anecdotal ! !
- off label use
- off formulary use

Gabapentin

- anticonvulsant
- structure related to gamma-aminobutyric acid
- mechanism of action ?
- used in other conditions including
  - pain
  - tremors
  - hot flushes
  - restless leg syndrome
  - various psychiatric disorders

Gabapentin

- open-label study 9 breast cancer pts
  - refractory nausea on AC with ondansetron + dexamethasone
- gabapentin 300 mg 3 x daily added
  - 5 days before
  - 6 days after chemo
- nausea rated on an 8-point scale


Gabapentin

- 6 reported at least a three-point improvement in peak delayed nausea (c.f. prior cycles)
- 3 patients had complete resolution of nausea
- no significant side effects
- gabapentin might have a role in treatment of chemotherapy-induced nausea
Gabapentin

Trials in progress - www.clinicaltrials.gov

- gabapentin (titrated to 300mg TDS Day 2 to 5) vs. aprepitant standard dose
- delayed nausea & vomiting associated with level 3, 4 or 5 emetogenic chemo
- patients who experienced delayed nausea +/- vomiting during their 1st cycle of chemotherapy

Conclusions - gabapentin & olanzapine

- the fact we are still searching reflects our inability to completely conquer chemotherapy-induced nausea/vomiting in every patient
- interesting results with agents licensed for other indications
- worth considering in patients with refractory emesis

Thank You