Cancer treatment induced nausea & vomiting

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Supportive Care Physician
The Christie NHS Foundation Trust
Disclosures

Previously undertaken paid work for:

- CHUGAI
- MSD
- ProStrakan
- KYOWA KIRIN
The Christie NHS Foundation Trust
Cancer Immunotherapy
Pseudomyxoma Peritonei
The landscape of cancer is changing.
More and more people are living longer with cancer.
Early access to supportive/palliative care can improve survival


2. Palliative and Supportive Care: Early Versus Delayed Initiation of Concurrent Palliative Oncology Care: Patient Outcomes in the ENABLE III Randomized Controlled Trial - Marie A. Bakitas, Journal of Clinical Oncology May 1, 2015:1438-1445; published online on March 23, 2015; DOI:10.1200/JCO.2014.58.6362

3. Effect of Early Palliative Care on Chemotherapy Use and End-of-Life Care in Patients With Metastatic Non–Small-Cell Lung Cancer; Joseph A. Greer, JCO; Feb 1 2012, vol 30, no 4, 394-400)
Supportive care [in cancer] is the prevention and management of the adverse effects of cancer and cancer treatment.
Proactive

Detect
symptoms early

Positive
approach: rebranding
ENHANCED SUPPORTIVE CARE

Integrating supportive care in oncology
(Phase I: Treatment with palliative intent)
Chemotherapy-induced nausea and vomiting (CINV)
Quality matters in CINV | Audit methods

n=360 patients

Prospective study of case notes and e-prescribing records

Disease sites
- Head & neck
- Breast
- Colorectal
- Ovarian

Followed through 3 cycles of chemotherapy

Data was collected on
- Severity of nausea and vomiting
- Anti-emetic use
- Hospital admission
- Concordance with international guidelines

Supportive Care Team, The Christie NHS Foundation Trust, CINV baseline audit, 2013-14
Quality matters in CINV | Headline results

- Males n =102, Females n=258
- Age range 27-86, mean 56, median 58 years
- Concordance with MASCC guidelines ranged from 88% (Head and Neck) to 0% (colorectal and ovarian)
- 57% of the total cohort reported nausea and 32% vomiting
- 11% of patients were admitted to hospital with CINV a contributory factor
- Aprepitant was added at a later cycle in 15% patients, which resulted in better symptom control (no further admissions in this group)
CLINICAL GUIDELINES

FOR THE PREVENTION AND MANAGEMENT OF CHEMOTHERAPY AND RADIOTHERAPY INDUCED NAUSEA AND VOMITING IN ADULTS

Supportive Care Team, The Christie NHS Foundation Trust, CINV clinical guidelines, 2015
What is CINV and why does it occur?
NEUROTRANSMITTERS AND ANTIEMETIC PATHWAYS:
Targeting Key Pathways to Influencing Emetic Control

DA = v dopamine; GABA = gamma-aminobutyric acid; NK = neurokinin; RAs = receptor antagonists
Physiology and neuropharmacology of chemotherapy-induced emesis

5-HT<sub>3</sub>, 5-hydroxytryptamine receptor type 3; chemo, chemotherapy; CTZ, chemoreceptor trigger zone; GI, gastrointestinal; NK<sub>1</sub>, neurokinin 1; VC, vomiting centre.

Artist rendering based on work of Paul Andrews and others.
Efficacy in controlling chemotherapy-induced emesis has progressed over the past 30 years.

5-day complete control:

- **Cisplatin (highly emetic)**
- **“AC” chemotherapy**

<table>
<thead>
<tr>
<th>Year</th>
<th>Cisplatin (%)</th>
<th>AC (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>1990</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td>2000</td>
<td>60</td>
<td>50</td>
</tr>
<tr>
<td>2010</td>
<td>85</td>
<td>75</td>
</tr>
</tbody>
</table>

AC, anthracycline + cyclophosphamide; RA, receptor antagonist.

Gralla R, personal communication.
Antiemetics in 2016: practical issues

1. Good – if not perfect – antiemetic agents are available
2. Quality evidence exists that should guide all oncologists in preventing “CINV”
3. Still, many patients experience emesis
4. Do evidence-based guidelines actually work?
5. If they do, can we enhance emetic prevention while addressing under use as well as over use?

CINV, chemotherapy-induced nausea and vomiting.
What is the burden of CINV?
CINV adversely impacts patients' quality of life

**Before chemotherapy (day 1)**  
Patients experiencing CINV (n = 68)  
Mean FLIE scores: 115

**After chemotherapy (day 3)**  
Patients without CINV (n = 54)  
Mean FLIE scores: 122 (n = 122)

FLIE, Functional Living Index–Emesis.

Patients believe that experiencing nausea and vomiting means their treatment is working

<table>
<thead>
<tr>
<th>Statement content</th>
<th>Agreed (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pt  I was afraid that tx for my CINV would cause problems with my other medicines</td>
<td>14.4</td>
<td>0.0007</td>
</tr>
<tr>
<td>HCP  I am concerned that tx for my patients’ CINV will cause problems with their other medicines</td>
<td>23.0</td>
<td></td>
</tr>
<tr>
<td>Pt  My CINV was an expected side-effect of my tx or disease so it is not a high priority</td>
<td>12.0</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HCP  CINV is an expected side effect of my patients’ tx or disease so it is not a high priority</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>Pt  It was more important for my provider to focus on curing my illness than to put time into CINV</td>
<td>18.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HCP  It is more important to focus on curing my patients’ illness than to put time into CINV</td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Pt  I didn’t want to bother my provider by bringing up my CINV</td>
<td>18.1</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HCP  I don’t want to bother my patients by bringing up the possibility of CINV</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Pt  Compared with the other problems I had, my CINV was not worth my attention</td>
<td>25.4</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HCP  Compared with the other tx-related side-effects my patients have, their CINV is a lower priority</td>
<td>3.6</td>
<td></td>
</tr>
<tr>
<td>Pt  In general, I tried to limit the number of medicines I took</td>
<td>63.2</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HCP  In general, I try to limit the number of medicines I prescribe</td>
<td>36.0</td>
<td></td>
</tr>
</tbody>
</table>

HCP, healthcare professional; pt, patient; tx, treatment.
Perceptions and reality: underestimation of emesis with chemotherapy

Physicians and nurses from 14 oncology practices in 6 countries

Patients: 72% women; 78% MEC; 49% breast cancer; 18% lung cancer

MD, physician; MEC, moderately emetogenic chemotherapy; RN, registered nurse.

Why optimal CINV treatment and prevention is important

- Nausea and vomiting are common and feared symptoms among cancer patients

- Up to 80% of patients will experience chemotherapy-induced nausea and vomiting (CINV) without prophylactic therapy

- Nausea and vomiting can lead to deteriorated nutritional status, compromise adherence to therapy, and impair quality of life irrespective of cause

- Inadequate emesis control may lead to anticipatory nausea and vomiting, which is a challenging clinical condition to treat and potentially refractory to standard medications
International CINV guidelines
Antiemetic guidelines evolution

- The ESMO/MASCC, NCCN and ASCO guidelines were developed in the late ‘90s

**Issue**
- Chemo triggering different CINV pattern and intensity
- Unclear efficacy of available antiemetics

**Solution**
- Classify chemo based on emetogenic potential
- Identify the best antiemetic prophylaxis for each emetogenic category

Perugia, Italy
Classify chemotherapy based on emetogenic potential

<table>
<thead>
<tr>
<th>Frequency of emesis (%)</th>
<th>Antiemetic guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 90</td>
<td>High (HEC)</td>
</tr>
<tr>
<td>30–90</td>
<td>Moderate (MEC)</td>
</tr>
<tr>
<td>10–30</td>
<td>Low</td>
</tr>
<tr>
<td>&lt; 10</td>
<td>Minimal</td>
</tr>
</tbody>
</table>

- The moderate class includes a broad range of emetogenic agents
- AC has been classified as HEC in ASCO and NCCN while it is classified as a special group of MEC in MASCC (“high MEC”)
- Carboplatin (MEC) could be reclassified as “high MEC” in the near future
- For selected patients with MEC agents, NCCN guidelines recommend the inclusion of aprepitant
<table>
<thead>
<tr>
<th>Emetic Risk Group</th>
<th>Representative Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGH</td>
<td>Cisplatin, Dacarbazine, Nitrogen Mustard</td>
</tr>
<tr>
<td>MODERATE</td>
<td>Anthracyclines, Carboplatin, Cyclophosphamide</td>
</tr>
<tr>
<td>LOW</td>
<td>Taxanes, Topoisomerase I Inhibitors, Mitoxantrone</td>
</tr>
<tr>
<td>MINIMAL</td>
<td>Chlorambucil, Vincas, Bleomycin</td>
</tr>
</tbody>
</table>
The strategy is to **prevent** nausea and vomiting, rather than treat

- complete control in all settings
- no side-effects
- convenient and easy to use
CINV: Acute and delayed phases
### Overview of NCCN/ASCO/MASCC-ESMO guidelines for acute nausea and vomiting

<table>
<thead>
<tr>
<th>Emetic risk group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>5-HT₃ + DEX + NK₁</td>
</tr>
<tr>
<td>Anthracycline + cyclophosphamide (AC)</td>
<td>5-HT₃ + DEX + NK₁</td>
</tr>
<tr>
<td>Moderate (other than AC)</td>
<td>PALO + DEX</td>
</tr>
<tr>
<td>Low</td>
<td>DEX OR 5-HT₃ OR DRA</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

**Legend:**
- 5-HT₃ = serotonin receptor antagonist
- DEX = dexamethasone
- NK₁ = neurokinin 1 receptor antagonist
- PALO = palonosetron
- DRA = dopamine receptor antagonist

*a* Some guideline groups combine “High” and “AC” into just one category, as “High”.

Overview of NCCN/ASCO/MASCC-ESMO guidelines for delayed nausea and vomiting

<table>
<thead>
<tr>
<th>Emetic risk group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>DEX + NK1(^b) or none</td>
</tr>
<tr>
<td>Anthracycline + cyclophosphamide (AC)</td>
<td>NK1(^b) or none ± DEX</td>
</tr>
<tr>
<td>Moderate (other than AC)</td>
<td>DEX</td>
</tr>
<tr>
<td>Low</td>
<td>No routine prophylaxis</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

\(^a\) Some guideline groups combine “High” and “AC” into just one category, as “High”; however, this presents a problem in delayed emesis because recommendations differ by category!

\(^b\) **NOTE**: if netupitant, rolapitant, or fosaprepitant 150 mg used on Day 1 – no further NK\(_1\), but continue NK\(_1\) if aprepitant is used on Day 1.
Revisiting the emetogenicity classification of chemotherapeutic agents

- Two current challenges regarding the emetogenicity classification of anti-cancer agents:
  - newer agents have not been evaluated for inclusion in the classification system
  - current category of MEC is very broad

- Consideration could be given to revisiting and redefining the MEC classification system, or to examining data from individual chemotherapeutic agents to identify those patients most likely to benefit from additional antiemetic prophylaxis with an NK$_1$ RA

Overall conclusions

- The principal sets of internationally recognized guideline recommendations consider PALO as the preferred 5-HT₃ RA with outperforming activity over ondansetron, granisetron, and dolasetron¹-³

- MASCC/ESMO Guidelines:¹
  - PALO is the recommended 5-HT₃ RA to be used in pure MEC setting
  - PALO is the preferred 5-HT₃ RA in AC regimens when a NK₁ RA is not available

- NCCN Guidelines:²
  - NEPA and rolapitant is recommended as an option for both HEC and MEC settings
  - While for the aprepitant and fosaprepitant option in MEC setting it is clearly specified that they should be added "for selected patients with additional risk factors or who have failed previous therapy with 5-HT₃ antagonist plus steroid", this note is not associated with NEPA
  - Palonosetron is the preferred 5-HT₃ RA choice in MEC setting

- ASCO Guidelines:³,⁴
  - NEPA + DEX is recommended as an additional treatment option in HEC and AC settings
  - PALO is the preferred agent in MEC setting

How effective are evidence-based guidelines in CINV?
Examples of studies examining the effectiveness of guidelines

Primary objective is to compare complete response rates over 5 days post-chemotherapy among patients receiving:

– guideline-consistent CINV prophylaxis (GCCP)

with those receiving:

– guideline-inconsistent CINV prophylaxis (GICP)

US registry ("INSPIRE") study: design and patients, using EHRs, MAT, and NCCN guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>1,295</td>
</tr>
<tr>
<td>Where conducted</td>
<td>4 oncology practice networks</td>
</tr>
<tr>
<td>Women (%)</td>
<td>70</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>59</td>
</tr>
<tr>
<td>HEC/AC/MEC (%)</td>
<td>11/25/64</td>
</tr>
<tr>
<td>Guideline compliant (%)</td>
<td>57</td>
</tr>
<tr>
<td>Guideline non-compliant (%)</td>
<td>43</td>
</tr>
</tbody>
</table>

EHR, electronic health record; MAT, MASCC Antiemesis Tool.

US registry ("INSPIRE") study: results, using EHRs, MAT and NCCN guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Guideline compliant</th>
<th>Guideline non-compliant</th>
<th>p value/odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>742</td>
<td>553</td>
<td>–</td>
</tr>
<tr>
<td>No CINV(^a) (%)</td>
<td>53</td>
<td>44</td>
<td>&lt; 0.001/1.31</td>
</tr>
<tr>
<td>No emesis</td>
<td>91</td>
<td>87</td>
<td>0.027/1.58</td>
</tr>
<tr>
<td>No nausea rate(^b) (%)</td>
<td>54</td>
<td>45</td>
<td>0.001/1.28</td>
</tr>
</tbody>
</table>

\(^a\)Defined as no emesis and no clinically significant nausea after receipt of chemotherapy.

\(^b\)Defined as a nausea score of less than 3 on a scale from 0 (no nausea) to 10 (most severe nausea).

Pan European Emesis Registry (“PEER”) study: design and patients using MASCC guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>991</td>
</tr>
<tr>
<td>Where conducted</td>
<td>8 European countries (including UK)</td>
</tr>
<tr>
<td>Women (%)</td>
<td>73</td>
</tr>
<tr>
<td>Median age (years)</td>
<td>57</td>
</tr>
<tr>
<td>HEC/AC/MEC (%)</td>
<td>19/47/34</td>
</tr>
<tr>
<td>Guideline compliant (%)</td>
<td>29</td>
</tr>
<tr>
<td>Guideline non-compliant (%)</td>
<td>71</td>
</tr>
</tbody>
</table>

Pan European Emesis Registry ("PEER") study: results using MASCC guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Guideline compliant</th>
<th>Guideline non-compliant</th>
<th>p value/odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (N)</td>
<td>287</td>
<td>704</td>
<td>–</td>
</tr>
<tr>
<td>Complete response(^a) (%)</td>
<td>60</td>
<td>51</td>
<td>0.008/1.43</td>
</tr>
<tr>
<td>No emesis (%)</td>
<td>63</td>
<td>59</td>
<td>0.154/1.18</td>
</tr>
<tr>
<td>No nausea(^b) (%)</td>
<td>48</td>
<td>41</td>
<td>0.031/1.37</td>
</tr>
<tr>
<td>No CINV (%)</td>
<td>43</td>
<td>34</td>
<td>0.016/1.41</td>
</tr>
</tbody>
</table>

\(^a\) No emesis or rescue therapy.

\(^b\) Defined as nausea scored < 5 on the VAS.

VAS, visual analogue scale.

Do clinical guidelines reduce clinician dependent costs?

George Kosimbei¹*, Kara Hanson² and Mike English³
Inclusion of patient related risk factors in the definition of CINV risk
Individual risk factors

- Female gender
- Young age (<50y)
- Anxious personality
- Minimal alcohol use (caveat ≥ 5 drinks/week is protective)
- History of emesis during pregnancy
- History of motion sickness
- History of previous CINV

From risk factors toward CINV prediction tools

- Patient-related risk factors
  - Younger age (<50 years)
  - No/minimal prior history of alcohol use

- Treatment-related risk factors
  - Impaired performance status
  - Emesis during pregnancy

Algorithm:
- Female gender
- Chemotherapy dose
- No/minimal prior history of alcohol use
- Younger age (<50 years)
- Emesis during pregnancy
- Use of moderate-to-high drug dose and multiple agents
- Susceptibility to motion sickness
- Anxiety
- Prior CINV
- Impaired performance status
- Previous exposure to chemotherapy

Actual probability of developing CINV
Patient-related factors contribute to emetic risk

- To approach antiemetic risk comprehensively, consideration should be given to both emetogenicity of the chemotherapy and the individual risk factors.

- However, the feasibility of such a model in routine practice might further complicate guideline recommendations/adherence.

- Further research such as prospective validation studies are needed.

* Questions for discussion.

Neurotransmitters and antiemetic pathways: targeting key pathways to influence emetic control

- GABA, gamma-aminobutyric acid.
- Histamine
- Dopamine/D2 RAs
- Endorphins
- Serotonin/5-HT3 RAs
- Acetylcholine
- Substance P/NK1 RAs
- Cannabinoids

GABA, gamma-aminobutyric acid.
5-HT\textsubscript{3} RAs

Examples of 5-HT\textsubscript{3} RAs approved for use as antiemetics

• Palonosetron
• Granisetron
• Ondansetron
• Dolasetron
## Binding affinity of 5-HT₃ RAs

<table>
<thead>
<tr>
<th>5-HT₃ RAs</th>
<th>pKᵢ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palonosetron¹</td>
<td>10.45</td>
</tr>
<tr>
<td>Granisetron²</td>
<td>8.42</td>
</tr>
<tr>
<td>Ondansetron²</td>
<td>8.07</td>
</tr>
<tr>
<td>Dolasetron³</td>
<td>7.55ᵃ</td>
</tr>
</tbody>
</table>

ᵃ pIC₅₀.
IC₅₀, half-maximal inhibitory concentration.

Ondansetron

• Medicines safety alert July 2013 re: prolongation of QTc interval & cardiac arrhythmias

• Useful resource: www.crediblemeds.org
Ondansetron

- Oral route now recommended
- IV dose to be diluted in over 65’s
- Palonosetron as alternative

<table>
<thead>
<tr>
<th>Moderate emetogenic potential – risk in 30 – 90% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre chemotherapy</strong></td>
</tr>
<tr>
<td><strong>Option 1:</strong></td>
</tr>
<tr>
<td>Ondansetron 8mg</td>
</tr>
<tr>
<td>IV/PO</td>
</tr>
<tr>
<td>Dexamethasone 7.6mg</td>
</tr>
<tr>
<td>IV / 8mg PO</td>
</tr>
<tr>
<td><strong>Option 2:</strong></td>
</tr>
<tr>
<td>Palonosetron 250micrograms IV</td>
</tr>
<tr>
<td>Dexamethasone 7.6mg</td>
</tr>
<tr>
<td>IV / 8mg PO</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>High emetogenic potential – risk in nearly all patients (&gt;90%) and Anthracycline &amp; Cyclophosphamide regimens</th>
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<tbody>
<tr>
<td><strong>Pre chemotherapy</strong></td>
</tr>
<tr>
<td>Ondansetron 8mg</td>
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<tr>
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</tr>
<tr>
<td>Dexamethasone 7.6mg</td>
</tr>
<tr>
<td>IV / 8mg PO</td>
</tr>
<tr>
<td>Aprepitant 125mg PO</td>
</tr>
</tbody>
</table>

*Following a drug safety update IV ondansetron must be administered as an infusion in 50-100ml of sodium chloride 0.9% over at least 15 minutes to all patients over 65 years of age due to the risk of prolongation of the QT interval.*
Metoclopramide

Drug Safety Update

Metoclopramide: risk of neurological adverse effects

From: Medicines and Healthcare products Regulatory Agency
Published: 7 August 2013
Therapeutic area: Anaesthesia and Intensive care, Cancer, Neurology, Paediatrics and neonatology, Pain management and palliation, and Radiology and imaging

Restricted dose and duration of use.
Metoclopramide

- Restricted dose & duration of use

<table>
<thead>
<tr>
<th>Low emetogenic potential - risk in 10 – 30% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pre chemotherapy</strong></td>
</tr>
<tr>
<td>No routine anti-emetics necessary</td>
</tr>
<tr>
<td><strong>On completion of chemotherapy</strong></td>
</tr>
<tr>
<td>No routine anti-emetics necessary, however, consider <strong>metoclopramide 10mg PO tds PRN 5/7</strong></td>
</tr>
</tbody>
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</tr>
<tr>
<td>Dexamethasone 7.6mg IV / 8mg PO</td>
</tr>
<tr>
<td><strong>On completion of chemotherapy</strong></td>
</tr>
<tr>
<td>Dexamethasone 4mg PO bd 2/7</td>
</tr>
<tr>
<td>Ondansetron 8mg PO bd 2/7</td>
</tr>
<tr>
<td><strong>Metoclopramide 10mg PO tds PRN 5/7</strong></td>
</tr>
<tr>
<td><strong>Option 2:</strong></td>
</tr>
<tr>
<td>Palonosetron 250micrograms IV</td>
</tr>
<tr>
<td>Dexamethasone 7.6mg IV / 8mg PO</td>
</tr>
<tr>
<td><strong>On completion of chemotherapy</strong></td>
</tr>
<tr>
<td>Dexamethasone 4mg PO bd 2/7</td>
</tr>
<tr>
<td><strong>Metoclopramide 10mg PO tds PRN 5/7</strong></td>
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</tr>
<tr>
<td><strong>Metoclopramide 10mg PO tds PRN 5/7</strong></td>
</tr>
<tr>
<td>Aprepitant 80mg PO od on days 2 &amp; 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial choice of prophylactic antiemetics in patients undergoing radiotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emetogenic risk</strong></td>
</tr>
<tr>
<td><strong>High</strong></td>
</tr>
<tr>
<td>Radiotherapy</td>
</tr>
<tr>
<td>TBI</td>
</tr>
<tr>
<td>Hemi body radiation</td>
</tr>
<tr>
<td>Radiotherapy to upper abdomen</td>
</tr>
<tr>
<td>Single fraction to lower thoracic or upper lumbar spine</td>
</tr>
<tr>
<td>Recommended treatment</td>
</tr>
<tr>
<td>Prophylaxis with ondansetron 8mg PO 30-60 minutes prior to treatment.</td>
</tr>
<tr>
<td><strong>Medium</strong></td>
</tr>
<tr>
<td>Fractionated abdominal or pelvic radiotherapy</td>
</tr>
<tr>
<td>Ondansetron 8mg PO 30-60 minutes prior to treatment OR</td>
</tr>
<tr>
<td><strong>Metoclopramide 10mg PO tds PRN OR</strong></td>
</tr>
<tr>
<td>Domperidone 10mg PO tds PRN</td>
</tr>
</tbody>
</table>
Domperidone

- Medicines safety alert May 2014 re: cardiac safety
- Restrict dose to 10mg tds for 7 days
- Contraindicated
  - Conduction abnormalities & CHF
  - Concomitant medicines known to prolong QTc ([www.crediblemeds.org](http://www.crediblemeds.org)) or potent CYP3A4 inhibitors
  - Severe hepatic impairment
Neurotransmitters and antiemetic pathways: targeting key pathways to influence emetic control

- GABA
- Histamine
- Endorphins
- Acetylcholine
- Cannabinoids
- Serotonin/5-HT$_3$ RAs
- Substance P/NK$_1$ RAs
- Dopamine/D$_2$ RAs
**NK₁ RA agents**

Approved or under investigation for use as antiemetics

- Aprepitant (oral)
- Fosaprepitant (i.v.)
- Netupitant (as oral NEPA)
- Rolapitant (oral)

i.v., intravenous; NEPA, netupitant and palonosetron.
NK-1 receptor antagonists
NK-1 RA

How do they work?

• NK1 receptors antagonists exert their strongest antiemetic properties through central inhibition of the emesis pattern generator (within the nucleus tractus solitarius)

• This is one of the final common mechanisms involved in activation and coordination of the vomiting reflex

• There is substantial evidence for involvement of substance P throughout the CINV response

• NK1 – RAs prevent the sensitisation of NK1 receptors by substance P

• This decreases the likelihood of vomiting

• NK-1 RAs also *increase the efficacy* of steroids and 5-HT$_3$ antagonists

So why is combination therapy important in CINV?

- The acute and delayed clinical time course of CINV has previously been linked to serotonin release and inflammation by the clinical effectiveness of 5-HT3 antagonists and steroids, respectively

- The discovery of the NK 1 receptor antagonists and clinical experience with these agents has furthered our understanding and provided substantial evidence for involvement of substance P throughout the CINV response

- The prolonged efficacy profile of many of NK-1 agents, including in the delayed phase, indicates that substance P acting at central NK-1 receptors becomes increasingly important with time in the pathophysiology of the overall CINV response

- These observations support the clinical rationale for combination therapy with 5-HT3 receptor antagonists (e.g., ondansetron), steroids (e.g., dexamethasone), and NK1 receptors antagonists to optimize control of CINV

Relevance of the NK$_1$ receptor pathway in the delayed phase

- NK$_1$ receptors are known to be involved in emesis by binding substance P$^1$

- Clinical data suggest that serotonin-dependent mechanisms predominate in the first 8–12 hours post-cisplatin, but thereafter, NK$_1$-dependent mechanisms become the dominant mediator in vomiting$^2$

- NK$_1$ RAs are thought to exhibit their delayed antiemetic activity mainly through central antagonism of NK$_1$ receptors in the dorsal vagal complex in the brainstem and area postrema$^3$

NK₁ RAs used in combination with 5-HT₃ RAs can better control acute and delayed CINV.

Time course of emesis following cisplatin with a 5-HT₃ RA or NK₁ RA

Patients free of emesis (%)

Time since cisplatin (h)

0 8 24 40 60 80 100 120

100 80 60 40 20 0

5-HT₃ RA + DEX + NK₁ RA
5-HT₃ RA + DEX
NK₁ RA + DEX

DEX, dexamethasone.

Palonosetron inhibition of 5-HT\textsubscript{3}/NK\textsubscript{1} receptor cross-talk

- It has been demonstrated that palonosetron uniquely inhibits cross-talk between the 5-HT\textsubscript{3} and NK\textsubscript{1} receptor pathways in a dose-dependent and time-dependent fashion.

- This differential inhibition of NK\textsubscript{1}/5-HT\textsubscript{3} cross-talk could explain palonosetron’s unique efficacy profile in delayed emesis.

Oncologists do not always prescribe 5-HT₃ RA with NK₁ RA

Q. While using an NK₁ product for the prevention of nausea and vomiting of HEC/MEC on the first day of chemotherapy, how do you prescribe it?

Use of an NK₁ RA on Day 1

<table>
<thead>
<tr>
<th></th>
<th>HEC</th>
<th>MEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>19% without 5-HT₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>68%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38% without 5-HT₃</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>53%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- I combine the NK1 with other antiemetics
- I prescribe the NK1 only (monotherapy)
- I combine the NK1 with DEX
- I combine the NK1 with a 5-HT3
- I combine the NK1 with a 5-HT3 and DEX

Data were collected by means of web-based interviews with a sample of 202 oncologists randomly selected from 4 EU countries (Italy, France, Germany, and UK). HEC, highly emetogenic chemotherapy, MEC, moderately emetogenic chemotherapy. Internal data on file. Source: IMS EU4 2015.
Steroids: How do they work in CINV?

- By reducing the permeability of the area postrema / CRTZ / blood brain barrier to emetogenic substances
- Depletion of GABA
The effect of adding dexamethasone to 5-HT₃ antagonists on acute emesis

Number of patients vomiting / number of patients evaluable

Test for heterogeneity
χ²-square = 15.1, df = 10; p>0.2
Dexamethasone dose

- Italian group for Antiemetic research
- Dose-finding study
- Dose ranges 4-20mg
- 20mg dose had highest efficacy
- Dose should be reduced to 12mg when used concomitantly with Aprepitant
Newer products in CINV
Akynzeo® (netupitant/palonosetron) use for CINV prevention

• **Akynzeo® is a fixed-dose combination of oral netupitant and oral palonosetron.**  

  1–3 Akynzeo is designed to improve antiemetic control by:
  – Administration as an all oral combination agent
  – A single dose schedule given on the day of chemotherapy only

• **Akynzeo® is licensed in the UK for:**
  – Acute and delayed nausea and vomiting associated with cisplatin-highly emetogenic chemotherapy
  – Acute and delayed nausea and vomiting associated with moderately emetogenic chemotherapy

• The characteristics of the two active pharmaceutical ingredients supported the development as a fixed combination, since their mechanism of action is exerted on different neuropathways (5-HT$_3$ receptors and NK$_1$ receptors) and both drugs show an extended half-life (approximately 40 and 90 hours for palonosetron and netupitant, respectively)$^2$

---

Efficacy and safety of NEPA for prevention of CINV following highly emetogenic chemotherapy: a randomised dose-ranging pivotal study

Phase 2, multicentre, randomised, double-blind, double-dummy, parallel group study (conducted at 29 sites in Russia and 15 sites in Ukraine in 2008)

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Treated (N=136)</th>
<th>Discontinued (N=1)</th>
<th>Efficacy analysis (N=136)</th>
<th>Safety analysis (N=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALO0.5 + DEX (20 mg) (N=136)</td>
<td>Treated (N=136)</td>
<td>Discontinued (N=1) Consent withdrawal</td>
<td>Efficacy analysis (N=136) Safety analysis (N=136)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEPA100 + DEX (12 mg) (N=135)</td>
<td>Treated (N=135)</td>
<td>Discontinued (N=1) Adverse event</td>
<td>Efficacy analysis (N=135) Safety analysis (N=135)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEPA200 + DEX (12 mg) (N=142)</td>
<td>Treated (N=138)</td>
<td>Discontinued (N=1) Adverse event</td>
<td>Efficacy analysis (N=137) Safety analysis (N=138)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NEPA300 + DEX (12 mg) (N=143)</td>
<td>Treated (N=136)</td>
<td>Discontinued (N=0)</td>
<td>Efficacy analysis (N=135) Safety analysis (N=136)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>*APR125 + OND32 + DEX (12 mg) (N=138)</td>
<td>Treated (N=134)</td>
<td>Discontinued (N=1) Lost to follow-up</td>
<td>Efficacy analysis (N=134) Safety analysis (N=134)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Exploratory arm (not powered for statistical analysis). APR: aprepitant; DEX: dexamethasone (given to all patients days 1–4); NEPA: fixed-dose combination of PALO + netupitant; OND: ondansetron; PALO: palonosetron. NEPA is licensed in 300 mg only.

Endpoints

Primary efficacy endpoint
• CR (no emesis, no rescue medication) during the overall (0–120 hour) phase

Secondary efficacy endpoints
• CR during the acute (0–24 hour) and delayed (25–120 hour) phases
• No emesis, no significant nausea (100 mm VAS score of <25 mm) and complete protection (CR and no significant nausea) during the acute, delayed and overall phases

Safety assessment
• Adverse events
• Clinical laboratory evaluations, vital signs, physical examination findings and ECGs

CR: complete response; ECG: electrocardiogram; VAS: visual analogue scale.
Complete response – Overall phase

- All NEPA dose groups showed statistically higher complete response (no emesis and no rescue) rates compared with palonosetron during the overall phase (0–120 hours)

*\(p\leq0.05\) from logistic regression versus PALO. †\(p\leq0.01\) from logistic regression versus PALO. ‡\(p\leq0.05\) from post hoc logistic regression versus PALO.

NEPA is licensed in 300 mg only. APR: aprepitant; NEPA: fixed-dose combination of PALO + netupitant; OND: ondansetron; PALO: palonosetron.

Overview of adverse events

- The overall incidence (≥2% incidence) type, frequency and intensity of treatment-emergent AEs were comparable across treatment groups.
- Of the 33 (4.9%) patients who experienced a severe AE, 9 (1.3%) were considered to be related to study treatments.
- One patient died during the study due to multiple organ failure (not considered to be due to study medication).

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>PALO (N=136)</th>
<th>NEPA\textsubscript{100} (N=135)</th>
<th>NEPA\textsubscript{200} (N=138)</th>
<th>NEPA\textsubscript{300} (N=136)</th>
<th>APR + OND (N=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any treatment-emergent AE</td>
<td>67 (49.3)</td>
<td>55 (40.7)</td>
<td>71 (51.4)</td>
<td>68 (50.0)</td>
<td>71 (53.0)</td>
</tr>
<tr>
<td>Treatment-related AE</td>
<td>17 (12.5)</td>
<td>18 (13.3)</td>
<td>24 (17.4)</td>
<td>21 (15.4)</td>
<td>26 (19.4)</td>
</tr>
<tr>
<td>Severe treatment-related AE</td>
<td>2 (1.5)</td>
<td>0 (0.0)</td>
<td>3 (2.2)</td>
<td>0 (0.0)</td>
<td>4 (3.0)</td>
</tr>
<tr>
<td>Serious treatment-related AE</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Treatment-related AE leading to discontinuation</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Total deaths</td>
<td>0 (0.0)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

NETU-08-18: Phase III study in patients receiving MEC

- Phase 3, multicentre, randomised, double-blind, double-dummy, parallel group study conducted at 177 sites in 15 countries (Apr 2011–Nov 2012)

- **Aim:** To demonstrate superiority of NEPA$_{300}$ over PALO in chemotherapy-naïve patients receiving AC-based moderately emetogenic chemotherapy (MEC) and to evaluate the safety of NEPA

<table>
<thead>
<tr>
<th>N=1,455 Randomised 1:1</th>
<th>Group</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PALO (n=725)</td>
<td>PALO 0.5 mg + DEX 20 mg</td>
</tr>
<tr>
<td></td>
<td>NEPA (n=724)</td>
<td>PALO 0.5 mg + NETU 300 mg + DEX 12 mg</td>
</tr>
</tbody>
</table>

- After completion of cycle 1, patients had the option to participate in a multiple-cycle extension, receiving the same treatment as assigned in cycle 1

AC: anthracycline (doxorubicin or epirubicin) + cyclophosphamide; MEC: moderately emetogenic chemotherapy; NEPA: fixed-dose combination of PALO + netupitant; PALO: palonosetron. DEX, dexamethasone; NETU, PALO and APR were administered 60 min prior to AC on Day 1; DEX was administered 30 min prior to chemotherapy on Day 1. Aapro et al. Ann Oncol 2014;25:1328-33
Complete response – Acute, delayed and overall phases

- NEPA was significantly superior to PALO during the acute, delayed and overall phases

Complete response (no emesis, no rescue medication)

**Acute (0–24 hour)**
- NEPA + DEX: 88.4%
- PALO + DEX: 85.0%
- **p=0.047**

**Delayed (25–120 hour)**
- NEPA + DEX: 76.9%
- PALO + DEX: 69.5%
- **p=0.001**

**Overall (0–120 hour)**
- NEPA + DEX: 74.3%
- PALO + DEX: 66.6%
- **p=0.001**

-----

DEX: dexamethasone; NEPA: fixed-dose combination of PALO + netupitant; PALO: palonosetron.
FLIE assessment: Nausea and vomiting

- A greater proportion of NEPA-treated patients reported no impact on daily living (NIDL) based on FLIE for the nausea, vomiting and combined domains compared with PALO

![Graph showing FLIE assessment results](image)

**Patients (%)**

- Nausea domain: NEPA + DEX 71.5%, PALO + DEX 65.8%
- Vomiting domain: NEPA + DEX 90.1%, PALO + DEX 84.4%
- Overall combined: NEPA + DEX 78.5%, PALO + DEX 72.1%

*p-values: 0.015, 0.001, 0.005*

**Notes:**
- DEX: dexamethasone; FLIE: Functional Living Index-Emesis; NEPA: fixed-dose combination of PALO + netupitant; PALO: palonosetron.
Higher CR rates with NEPA maintained across 4 cycles of chemotherapy

- CR rates (overall 0–120 h) for during the first 4 treatment cycles

\[
\begin{array}{c|c|c|c|c}
\text{Cycle} & \text{NEPA + DEX} & \text{PALO + DEX} & \text{p-value} \\
\hline
1 & 74 & 67.0 & 0.001 \\
2 & 80 & 67.0 & <0.0001 \\
3 & 84 & 70.0 & <0.0001 \\
4 & 84 & 75.0 & <0.0001 \\
\end{array}
\]

76% of patients completed at least 4 cycles. CR: complete response; DEX: dexamethasone; NEPA: fixed-dose combination of PALO + netupitant; PALO: palonosetron.
Conclusions from Akynzeo® randomised trials

• Netupitant at 300 mg is an appropriate NK₁ RA to add to palonosetron in an all oral combination. This dose was associated with few side effects and high efficacy

• The addition of netupitant significantly improves the efficacy of palonosetron

• Akynzeo® as a single dose regimen given only prior to chemotherapy (with dexamethasone on day 1) is effective:
  – In patients receiving MEC, such as anthracycline + cyclophosphamide, as for breast cancer and requires no further antiemetic agents after day 1
  – In patients HEC, such as cisplatin, with only dexamethasone continued after day 1

• Akynzeo® is well tolerated and maintains efficacy over repeated cycles of chemo

• Akynzeo® provides a straight-forward strategy to enhance the use of guideline-based antiemetic regimens and is maximally convenient to improve patient adherence
Rolapitant*: A new NK₁ Receptor Antagonist

- Background and Results -

• The metabolic route is an important differentiating factor
  • Major metabolism is not via CYP 3A4 (others induce CYP3A4)
  • Re-assuring for some oncologists and P & T committees
  • Potential in future investigation for exploring other – and higher – dosing regimens which could improve efficacy

• Rolapitant performed well in its licensing trials
  • Consistency of efficacy and safety, across trials and across the chemotherapy tested (Highly and Moderately Emetic)

*Not licensed in the UK

OLANZAPINE AS AN ANTIEMETIC
- Background and Overview -

- Olanzapine is an antipsychotic agent available orally
- It affects a variety of neurotransmitter receptors
- Multiple phase II and phase III trials have indicated antiemetic activity
- Studies have often had small sample sizes, were not always double-blinded and were of low power
- Side effects include sedation at a higher level than with other agents
- What is its role?:
  - Initial therapy as a replacement for an NK₁RA, or
  - As the 4th drug in a combination, or
  - In a regimen in patients who have not done well on the first cycle (or breakthrough CINV)
OLANZAPINE 4-AGENT PHASE III Alliance 221301 TRIAL
- Randomized, Double-Blind Study-

- Cisplatin ≥ 70 mg/M² or Cyclophosphamide / Doxorubicin (600 / 60 mg/M²)

- **Antiemetics:** 3 Drugs for All: 1) Aprepitant or Fos-aprepitant + 2) Dexamethasone x 3 days + 3) 5HT₃ Receptor Antagonist of choice. *All antiemetics given PO*

- PLUS either: Olanzapine 10 mg / day on days 1 – 4, OR Placebo on days 1 - 4

<table>
<thead>
<tr>
<th></th>
<th>3-Drugs + Olanzapine (n = 192)</th>
<th>3-Drugs + Placebo (n = 188)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Nausea: Acute / Delayed</td>
<td>74% / 42%</td>
<td>45% / 24%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Complete Response: Acute / Delayed</td>
<td>86% / 67%</td>
<td>65% / 52%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Sedation on day 2**: &gt; 5 (scale 0 – 10)</td>
<td>20%</td>
<td>7%</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>

- **Side Effects:** Grade 3 or 4 Adverse Events: Olanzepine 6%; Placebo 2%

* CR = No emesis and no use of rescue  ** Day of maximal sedation.

Sancuso®
(Granisetron Transdermal System)
Sancuso (Granisetron patch)

- Licensed for CINV
- Where swallowing difficulties
- Up to 7 days effective
- Releases 3.1mg granisetron / 24h
- Apply 24-48h pre-chemo
- Better side effect profile ct. oral granisetron
Ginger

• As an aid to reducing nausea during chemotherapy

• 5 RCTs – 3 benefit, 2 negative

• Doses 500-1500mg daily added to anti-emetic regime
Final thoughts
The objective of antiemetic therapy is the **complete prevention of CINV**

- Treatment should individualise to the patient’s regimen and other factors such as physical and psychological comorbidity
- Patients should have access to information and alternative treatments
- Admission as a consequence of CINV should be considered as a treatment failure (?Serious Untoward Incident)
- Where control is poor other causes such as CNS or gastrointestinal pathology, metabolic problems, and drugs should be considered prior to changing antiemetics
- In our Centre the introduction of MASCC guidance, comprehensive clinical assessment prior to and after the first cycle (with the early addition of aprepitant for symptomatic patients), could reduce debilitating symptoms, improve QOL, and reduce unnecessary admissions
Incorporating Effective Supportive Care into Anticancer Treatment and Research: Some Conclusions

• Skilled supportive care should be extended to all
  • Integral part of the mission of modern oncology

• Broad spectrum *appropriate* supportive care contributes to:
  • Quality of life
  • Possibly to survival, but definitely to the quality of that survival

• Proper care allows the use of superior anticancer regimens

• Antiemetics continue to be crucial in patients receiving most combination chemotherapy regimens:
  • Preserve quality of life
  • Permit out-patient treatment
  • Reduce or eliminate associated symptoms and side-effects
  • Enhance use of the most effective antineoplastic agents
“...Cancer patients are living longer and better lives, thanks to better symptom control, more effective therapies, and a deeper understanding of cancer...”

Dr Harold Varmus,
Director NCI, PBS Newshour, 24 September 2012.