Optimizing CINV management: applying evidence in clinical practice

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“…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, September 24, 2012
At the beginning of the 1990s, we did not have effective prevention and treatment of CINV.

Nausea and vomiting significantly decreased the quality of life…
What are the current treatment options?

**5-HT₃ RA**
- Ondansetron
- Granisetron
- Dolasetron
- Palonosetron

**Corticosteroids**
- Dexamethasone

**NK₁ RA**
- Aprepitant
- Fosaprepitant
- Netupitant (NEPAᵃ)
- Rolapitant

**Multi-receptor**
- Olanzapine

Guideline-recommended triplet antiemetic combination¹–³


ᵃ NEPA, fixed combination of netupitant (300 mg) and palonosetron (0.50 mg).

5-HT₃, 5-hydroxytryptamine type 3; DEX, dexamethasone; ESMO, European Society for Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; NCCN, National Comprehensive Cancer Network; NK₁, neurokinin 1; RA, receptor antagonist.
…but how many situations are really standard?
Question 1

Have you ever met a patient who is experiencing vomiting after chemotherapy even though a standard preventive treatment had been given?

1) Yes

2) No

3) Not applicable
Evidence from the “real world” clinical setting

Number of CT cycles = 4,197.
Missing data: acute vomiting 3.6%; acute nausea 3.2%; delayed vomiting 4.2%; delayed nausea 4.2%.


*h, hours.*
Patient case: RL

- RL is a 60-year-old female with a new diagnosis of metastatic NSCLC
- She is a smoker and drinks 1-2 alcoholic drinks/week
- RL has had three pregnancies involving hospitalization for morning sickness
- She also has a significant medical history of depression, hypothyroidism, anxiety, impaired glucose tolerance, and GERD

- She will receive her 1st cycle of chemotherapy:
  - Cisplatin 75 mg/m² i.v. on Day 1
  - Etoposide 100 mg/m² i.v. on Days 1–3

- This regimen will be given every 28 days for 4–6 cycles

GERD, gastroesophageal reflux disease; NSCLC, non-small-cell lung cancer.
Question 2

What is the optimal tailoring approach to preventing CINV?

1) According to the patient's wishes

2) Provide treatment based on patient-related and regimen-based risk factors

3) Utilize standardized institution-specific antiemetic guidelines

4) Postpone treatment until symptoms occur
CINV risk assessment tool for establishing overall emetic risk

- Patient risk factors
- Regimen risk factors

Overall emetic risk
### Regimen-specific risk factors: emetogenic potential of anticancer agents

<table>
<thead>
<tr>
<th>Level</th>
<th>Frequency of emesis (%)</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High (i.v. agents)</strong></td>
<td>&gt; 90</td>
<td>• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide</td>
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<td></td>
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<td>• Carboplatin AUC ≥ 4</td>
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<td>• Carmustine &gt; 250 mg/m²</td>
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<td>• Cisplatin</td>
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<td>• Cyclophosphamide &gt; 1,500 mg/m²</td>
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<td>• Dacarbazine</td>
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<td></td>
<td></td>
<td>• Doxorubicin ≥ 60 mg/m²</td>
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<td>• Epirubicin ≥ 90 mg/m²</td>
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<td></td>
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<td>• Ifosfamide ≥ 2 g/m²/dose</td>
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<td>• Mechlorethamine</td>
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<td></td>
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<td>• Streptozocin</td>
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<td><strong>Moderate (i.v. agents)</strong></td>
<td>30–90</td>
<td>• Bendamustine</td>
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<td>• Carboplatin AUC &lt; 4</td>
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<td></td>
<td></td>
<td>• Carmustine ≤ 250 mg/m²</td>
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<td></td>
<td></td>
<td>• Cyclophosphamide ≤ 1,500 mg/m²</td>
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<td></td>
<td></td>
<td>• Cytarabine &gt; 200 mg/m²</td>
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<td></td>
<td></td>
<td>• Daunorubicin</td>
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<td></td>
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<td>• Doxorubicin &lt; 60 mg/m²</td>
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<td>• Epirubicin ≤ 90 mg/m²</td>
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<td>• Ifosfamide &lt; 2 g/m²/dose</td>
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<td>• Irinotecan</td>
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<td>• Melphalan</td>
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<td></td>
<td></td>
<td>• Methotrexate ≥ 250 mg/m²</td>
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<td>• Oxaliplatin</td>
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<td></td>
<td></td>
<td>• Temozolamide</td>
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<td><strong>Low (i.v. agents)</strong></td>
<td>10–30</td>
<td>• 5-fluorouracil (5-FU)</td>
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<td>• Ado-trastuzumab emtansine</td>
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<td></td>
<td></td>
<td>• Cytarabine 100–200 mg/m²</td>
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<td>• Docetaxel</td>
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<td></td>
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<td>• Doxorubicin (liposomal)</td>
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<td>• Gemcitabine</td>
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<td>• Paclitaxel</td>
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<td>• Pemetrexed</td>
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<td>• Ziv-aflibercept</td>
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<td><strong>Oral agents with moderate to high</strong></td>
<td>≥ 30</td>
<td>• Alotretamine</td>
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<td>• Busulfan ≥ 4 mg/d</td>
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<td>• Ceritinib</td>
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<td>• Crizotinib</td>
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<td>• Cyclophosphamide ≥ 100 mg/m²/d</td>
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<td>• Estramustine</td>
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<td>• Etoposide</td>
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<td>• Lenvatinib</td>
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<td>• Lomustine (single day)</td>
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<td>• Mitotane</td>
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<td>• Panobinostat</td>
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<td>• Procarbazine</td>
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<td></td>
<td></td>
<td>• Rucaparib</td>
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<td></td>
<td></td>
<td>• Temozolomide &gt; 75 mg/m²/d</td>
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</tbody>
</table>

*See guidelines for complete updated lists of emetic risk categories, including minimal level (< 10% frequency of emesis). AUC, area under the curve; i.v., intravenous.*

Predictive factors for optimizing selection of prophylactic antiemetics

- 8 risk factors identified:
  1) Patient age < 60 years
  2) The first 2 cycles of chemotherapy
  3) Anticipatory nausea and vomiting
  4) History of morning sickness
  5) Hours of sleep the night before chemotherapy
  6) CINV in the prior cycle
  7) Patient self-medication with non-prescribed treatments
  8) Use of platinum or AC-based regimens

Patient case: RL

• RL is a 60-year-old female with a new diagnosis of metastatic NSCLC
• She is a smoker and drinks ~1-2 alcoholic drinks/week
• RL has had three pregnancies involving hospitalization for morning sickness
• She also has a significant medical history of depression, hypothyroidism, anxiety, impaired glucose tolerance, and GERD

• She will receive her 1st cycle of chemotherapy:
  – Cisplatin 75 mg/m² i.v. on Day 1
  – Etoposide 100 mg/m² i.v. on Days 1–3

• This regimen will be given every 28 days for 4–6 cycles

Question 3

What kind of antiemetic regimen would you choose for RL?

1) $5\text{-HT}_3$ RA + DEX + metoclopramide

2) $5\text{-HT}_3$ RA + NK$_1$ RA + DEX + lorazepam

3) NK$_1$ RA + DEX + metoclopramide
Recommended antiemetic assessment and treatment plan for RL: HEC

For acute CINV:
- NK₁ RA
- 5-HT₃ RA
- DEX

For delayed CINV:
- DEX on Days 2–4
- APR Days 2, 3
  (if given on Day 1)
- Patient-specific assessment due to diabetes risk and corticoids

Patient case: AS

• AS is a 42-year-old female
• She is a teacher at a local elementary school
• She presents with 3-month history of fatigue and a > 4 kg unintentional weight loss
• Never smoked, does not drink alcohol
• Three children, history of significant morning sickness with 3rd child
• Colonoscopy revealed 8 cm caecal tumour
• Biopsy confirmed diagnosis of colorectal adenocarcinoma with KRAS mutation

• Treatment: m-FOLFOX6 + bevacizumab
  – AS will receive this regimen q2w for 6 cycles
  – FOLFOX: oxaliplatin + folinic acid + 5-fluorouracil
Question 4

Based on the guidelines, which antiemetic regimen is recommended for AS?

1) 5-HT$_3$ RA + DEX

2) NK$_1$ RA + PPI + H1 antagonist

3) Institution-based protocol

4) None of the above

PPI, proton pump inhibitor.
Recommended antiemetic assessment and treatment plan for AS: MEC

For acute CINV:
- 5-HT₃ RA + DEX

For delayed CINV:
- DEX on Days 2, 3
- No treatment in patients with low risk of CINV

5-HT₃ RAs
- DOL, GRAN, OND, PALO
  - PALO and GRAN extended-release injection are preferred in NCCN¹
  - PALO has longer half-life vs other 5-HT₃ RAs²
  - PALO is specifically approved for the prevention of nausea and vomiting³

DOL, dolasetron; GRAN, granisetron; MEC, moderately emetogenic chemotherapy; PALO, palonosetron; OND, ondansetron.

Patient case: AS (cont.)

- During cycle 1, AS continues to experience nausea and vomiting in the days following chemotherapy
- She reports developing additional symptoms
  - Weight loss of 3 kg
  - Depression
  - Fatigue
Question 5

Which is considered a risk factor for developing CINV?

1) Age < 60 years

2) Anticipatory nausea and vomiting

3) CINV in the previous cycle

4) History of morning sickness

5) All of the above
How would you modify her antiemetic regimen?

• What further recommendations would you make?
  – Addition of NK₁ RA to 5-HT₃ RA + DEX
  – In consideration of busy schedule with 3 small children and teaching responsibilities, NEPA single-dose for convenience
How can adherence to antiemetic guidelines be improved in your practice?

- Suggested approaches from ONS survey
  - **Education** of providers
    - Physicians
    - Nurses
    - Pharmacists
  - Use **standardized protocols** and orders
  - Improve patient teaching
  - Follow-up

ONS, Oncology Nursing Society.

Message for clinical practice

- **Prevention** of CINV is better than symptomatic treatment
- Follow the **guidelines** for prevention of CINV, based on the emetogenicity of chemotherapy regimens
- Additionally, take each patient’s **individual risk factors** and **comorbidities** into account
- **New therapeutic options** offer the opportunity to improve guideline adherence and ensure a **better quality of life**
  - NK₁ RAs and fixed-combination (NEPA)
- Applying effective **therapeutic** strategies as indicated for nausea and vomiting will result in **improved adherence to cancer treatment**
The way is tailoring…

Images available from: