Updates in the Management of Chemotherapy-induced Nausea and Vomiting (CINV)

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Objectives
• Review recently approved drugs in the management of CINV
• Discuss select recent landmark trials for new drugs in the management of CINV
• Summarize key updates to evidence and practice based guidelines on the management of CINV

Impact of CINV
• Medical complications
  ▫ Dehydration, electrolyte imbalances, hospitalization
  ▫ Poor nutrition, weight loss
• Disruption, delay or noncompliance to chemotherapy
• Decline in performance status and mental status
• Impaired quality of life and physical well being

Introduction
• One of the top feared and distressing side effect of chemotherapy
• 70% - 80% of all patients receiving chemotherapy without appropriate prophylaxis will develop CINV
• Even with prophylaxis, up to 35% of patients will develop acute CINV & ~54% develop delayed CINV

Definitions
• Acute CINV
  ▫ Occurs within the first 24hrs of chemotherapy
• Delayed CINV
  ▫ Occurs 24hrs after chemotherapy and lasts up to 7 days
• Anticipatory CINV
  ▫ Occurs before chemotherapy administration, usually triggered by sight, sound or smell
  ▫ Due to poor control of CINV in previous cycles
• Breakthrough CINV
  ▫ Occurs despite adequate/appropriate prophylaxis, often needing rescue medications

Disclosures
• No disclosures or conflict of interest
Pathophysiology

Risk factors

Patient Specific
- Age (younger > older)
- Gender (women > men)
- Low alcohol consumption
- Emesis with prior chemo
- History of motion sickness or morning sickness
- Psychosocial factors: anxiety, depression, distress

Treatment Specific
- Emetic risk category of chemotherapy regimen
- Chemotherapy dose
- Chemotherapy schedule (combination & rate)
- Chemotherapy in combination with radiation

Overall emetic risk = Patient risk factors + regimen risk factors

Chemotherapy Emetic Risk Category

<table>
<thead>
<tr>
<th>Category</th>
<th>Emetic Risk</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (HEC)</td>
<td>Risk in nearly all patients (&gt;90%)</td>
<td>Cisplatin, cyclophosphamide &gt;1500mg/m², doxorubicin&gt;60mg/m²</td>
</tr>
<tr>
<td>Moderate (MEC)</td>
<td>Risk in 30% to 90% of patients</td>
<td>Carboplatin, oxaliplatin, busulfan, melphalan, irinotecan, idarubicin</td>
</tr>
<tr>
<td>Low</td>
<td>Risk in 10% to 30% of patients</td>
<td>Docetaxel, etoposide, 5-FU, gemcitabine, paclitaxel, topotecan</td>
</tr>
<tr>
<td>Minimal</td>
<td>Fewer than 10% at risk</td>
<td>Bortezomib, decitabine, nelumab, bleomycin, bevacizumab</td>
</tr>
</tbody>
</table>

HEC: High emetic risk category
MEC: Moderate emetic risk category

Agents used in CINV
- Neurokinin receptor antagonists
  - Aprepitant, fosaprepitant
- 5HT-3 receptor antagonists
  - Palonosetron, ondansetron, granisetron, dolasetron
- Corticosteroids
  - Dexamethasone
- Dopamine antagonists
  - Metoclopramide, promethazine, prochlorperazine, haloperidol
- Others
  - Lorazepam, dronabinol, diphenhydramine, scopolamine

Poll Question
1. Which of the following drugs were recently approved by the FDA for the prevention and/or treatment of CINV?
   - A. Varubi® (Rolapitant)
   - B. Sustol® (Granisetron ER)
   - C. Syndros® (Dronabinol solution)
   - D. All of the above
   - E. A & B only

What's New?
Ondansetron Oral Film (Zuplenz®)

- Ondansetron oral soluble film
  - Rapidly dissolves in mouth in 10 secs
  - Pleasant peppermint flavor with no gritty aftertaste
  - Eliminates the burden of swallowing pills
- Clinically bioequivalent to ondansetron orally disintegrating tablets (ODT)
  - Same efficacy and side effect profile
- Available in same doses as zofran: 4mg, 8mg

Netupitant/Palonosetron (Akynzeo®)

- Oral single dose fixed combination of netupitant (300 mg) and palonosetron (0.50 mg)
- Netupitant
  - Novel highly selective NK₁ receptor antagonist (RA)
  - High brain penetration
  - Long half life of ~90hrs vs aprepitant ~9-13 hrs
- Palonosetron
  - Second generation 5HT₃RA
  - Long half life of ~40 hrs

Netupitant/Palonosetron (NEPA)

- NEPA synergically prevents the NK₁ receptor response against substance P
  - Additive effect on NK₁ receptor internalization
- Substrate and moderate inhibitor of CYP3A4
  - Dose adjustments when given with other CYP3A4 substrates (dexamethasone)
- No interactions with CYP2C9 substrates and chemotherapy agents that are CYP3A4 substrates

Safety Profile of NEPA

- Comparable safety profile to aprepitant/palonosetron
- Most common treatment related ADEs
  - Constipation (3.6%)
  - Headaches (1%)
- Cardiac adverse effects
  - Most frequent ECG change was flat T waves (17%) and ST depression (12%)
- Few treatment related ADEs and discontinuations

Rolapitant (Varubi®)

- Novel highly selective long acting oral NK₁-RA
- Long half life of ~180 hours
  - NK₁-receptor occupancy >90% in cortex and 73% in striatum 5 days after single oral dose
- Oral single dose of 180mg (two 90mg)
  - Given 1-2 hours before chemotherapy
- NDA application submitted for intravenous (IV) formulation
Rolapitant (Varubi®)

- Does not induce/inhibit CYP3A4 but inhibits CYP2D6
  - No dose adjustments required with dexamethasone or other drugs metabolized by CYP3A4
- Contraindicated in patients receiving thioridazine, a CYP2D6 substrate.
  - QT prolongation and Torsades de Pointes
- Avoid other CYP2D6 substrates with narrow therapeutic index
  - Inhibitory effect on CYP2D6 lasts for at least 7 days

Rolapitant Clinical Trials

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapoport et al</td>
<td>D1: ROLA 180mg + GRA 10μg/kg IV + DEX</td>
<td>OR - CR (No nausea, no rescue antiemtic) HEC-1: 7.7% vs 58%; OR 1.3, p=0.0016 HEC-2: 7.0% vs 62%; OR 1.4, p=0.0426 Pooled studies: 7.8% vs 60%; OR, p=0.001</td>
</tr>
<tr>
<td>Schwartzberg et al</td>
<td>ROLA 180mg + GRA 2mg + DEX</td>
<td>-CR (No nausea, no rescue antiemtic in delayed phase) IV: 71% vs 62%, p=0.0002 Overall phase: 59% vs 58%, p=0.0001 Acute phase (83% vs 80%, p=0.14) No difference in acute phase</td>
</tr>
</tbody>
</table>

Safety Profile of Rolapitant

- Safety profile comparable to other NK1,RA
  - Few treatment related ADEs and discontinuations
- Do not administer at less than 2-week interval
- Avoid CYP2D6 substrates (pimozide, thioridazine)
- Most common treatment related ADEs
  - Constipation, headaches, hiccups, dyspepsia

Dronabinol Oral Solution (Syndros®)

- Liquid version of Marinol (dronabinol) soft gel capsules
- Flexible administration option
  - Allows for rapid absorption
  - Easy titration to clinical effects
  - Lower intra-patient variability
- Active ingredient: tetrahydrocannabinol (THC)
- Available as 5mg/ml solution
  - Recommended starting dose is 4.2mg/m²
    - 1 - 3 hours prior to chemo, then every 2 - 4 hours after for a total of 4 to 6 doses per day.

Dronabinol Oral Solution (Syndros®)

- Approved for CINV in patients who have failed conventional antiemetic treatments
  - Also approved for anorexia associated with weight loss in patients with AIDS
- Approval based on bioequivalence/pharmacokinetics compared with marinol
**Safety Profile of Syndros®**

- Similar safety profile with marinol
- **Warnings/precautions:**
  - Psychiatric and cognitive effects which may impair mental and/or physical abilities
  - Hypotension, hypertension, syncope, or tachycardia in patients with cardiac disorders
  - Interaction with disulfiram and metronidazole
  - Hold products with disulfiram or metronidazole at least 14 days before administration and 7 days after treatment
  - Seizures in patient with seizure history

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**Granisetron ER (Sustol®)**

- Novel extended release subcutaneous granisetron
- Biochromon polymer based delivery system providing therapeutic concentrations for ≥ 5 days
  - Contains 2% granisetron and a polymer vehicle
  - Controlled hydrolysis resulting in slow controlled and sustained release of drug
  - Available as a 10mg/0.4ml single dose prefilled syringes
  - At least 30 minutes before chemotherapy on days 1

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**Granisetron ER (Sustol®)**

- Administration by health care provider only
  - Administer in upper arm of skin or abdomen
  - Requires slow sustained injection due to high viscosity
  - Do not give more frequently than once every 7 days
  - Renal Adjustments:
    - Moderate (Clcr 30-59ml/min): Give every 14 days
    - Severe (Clcr <30ml/min): Do not use

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**Sustol® Clinical Trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raftopoulos H et al (Phase III RCT MEC=669 HEC=735)</td>
<td>D1: APF350 5mg or APF350 10mg + DEX D2: DEX</td>
<td>Noninferiority to palonosetron during acute and superiority on delayed phase (CR) Acute CR (MEC): 74.8%,76.9% vs 71.7%,73.6% (p=0.036) Delayed MEC: 58.3% vs 57.3% (95.12%) APF350 was not superior to palonosetron during delayed phase but noninferior</td>
</tr>
<tr>
<td>Schneidt et al (MAGIC) Phase III RCT (n=962) HEC</td>
<td>D1: APF350 10mg + DEX D2: DEX</td>
<td>D2: DEX CR (No emesis, no rescue antiemetics) in delayed phase (24-120h) Delayed phase: 64.3% vs 56.8%, p=0.014 Overall phase: 58.4% vs 52.9%, p=0.002 Acute phase (75% vs 73%, p=0.502) No difference in acute phase</td>
</tr>
</tbody>
</table>

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**Safety Profile of Sustol®**

- Similar safety profile with other 5HT3 antagonist
- **Warnings/precautions:**
  - Injection site reactions (IRS)-Can occur 2 weeks or more after administration
    - Increased risk of bruising/hematoma with anticoagulants and antiplatelet
  - Gastrointestinal: constipation, decreased bowel activity
  - Most common adverse reactions (≥ 3%)
    - IRS, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia

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**Olanzapine (Zyprexa®)**

- Atypical antipsychotic
- Second generation thienobenzodiazepine
- Initially approved in 1996 for psychotic disorders
- Not FDA approved for CINV
- Attractive drug as it targets many receptors
  - Dopaminergic (D1, D2, D3, D4), serotonergic (5-HT2A, 5-HT2C, 5-HT3, 5-HT6), adrenergic, histaminergic (H1), and muscarinic (m1, m2, m3, m4) receptors.
**Pathophysiology**

CNS

- Stress
- Cytokines
- Inflammation

GLANZAPINE

- GLANZAPINE

**Olanzapine Clinical Trials**

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment Regimen</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navari et al.</td>
<td>OLP: D1: OLP 10mg + DEX</td>
<td>- CR (No emesis, no rescue antiemetic) p&lt;0.05</td>
</tr>
<tr>
<td></td>
<td>Placebo + DEX</td>
<td>- Primary endpoint (No nausea after chemo)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 24hrs: 74% (OLP) vs 46% (5mg) 0.001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- 25-120hrs: 42% vs 25% p&lt;0.003</td>
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<tr>
<td></td>
<td></td>
<td>- 1-120hrs: 37% vs 22% p=0.002</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- CR (No emesis, no rescue antiemetic)</td>
</tr>
</tbody>
</table>


**Olanzapine Dosing**

- Several doses and duration have been studied
- Standard dosing: 10mg daily (max:20mg/day)
- Lower doses (5mg) may be used for select patients
- No loading dose, start 1 day to 3 days 1/4 of chemotherapy
- Effective in treating breakthrough CINV
- 10mg daily for 3 days
- Best olanzapine containing regimen?
  - Quadruple regimen (OLP + NK1 + 5HT3 + DEX)
  - Triple regimen (Substitute OLP for NK2 or SHT3)

**Safety Profile of Olanzapine**

- Good safety profile
  - No grade 3 or 4 adverse drug reactions in studies
- Most common adverse effects
  - Fatigue, sedation, drowsiness, somnolence, disturbed sleep, sedation, increased appetite, weight gain
- Use with caution in special populations
  - Elderly patients
  - Concurrent medications that depress CNS (lorzepam)

**Price Comparison of New Agents**

<table>
<thead>
<tr>
<th>Agent</th>
<th>AWP Package Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron oral film (Zuplenz)</td>
<td>~$32/dose (1 oral film)</td>
</tr>
<tr>
<td>Dronabinol solution (Syndros)</td>
<td>Not available</td>
</tr>
<tr>
<td>Netupitant/Palonosetron (NEPA)</td>
<td>$659/dose (1 tablet)</td>
</tr>
<tr>
<td>Rolapitant (Varubi)</td>
<td>$636/dose (2 tablets)</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa)</td>
<td>~$20/tablet</td>
</tr>
<tr>
<td>Granisetron (Zofran)</td>
<td>$594/dose</td>
</tr>
</tbody>
</table>
Poll Question

1. Which of the following statements are false?
   A. Dose reductions are necessary when administering rolapitant with other CYP3A4 substrates
   B. Olanzapine was recently FDA approved for the prevention of CINV
   C. Patient may inject self with Sustol® before presenting to clinic for day 1 of chemotherapy
   D. Renal dose adjustments are not necessary for Sustol®
   E. All of the above

CINV Guidelines

- Evidence based guidelines
  - MASCC/ESMO: Multinational Association of Supportive Care in Cancer/European Society for Medical Oncology
  - ASCO: American Society of Clinical Oncology
- Practice based guidelines
  - NCCN: The National Comprehensive Cancer Network

CINV Guidelines

<table>
<thead>
<tr>
<th></th>
<th>ASCO</th>
<th>MASCC/ESMO</th>
<th>NCCN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expert Panel</td>
<td>Select ASCO members</td>
<td>Select members across several countries/continents</td>
<td>Select members from NCCN member institutions</td>
</tr>
<tr>
<td>Last Updated</td>
<td>Nov 2015</td>
<td>March 2016</td>
<td>April 2016</td>
</tr>
<tr>
<td>Methodology</td>
<td>Evidence based</td>
<td>Evidence based</td>
<td>Consensus based</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>Multinational -5 continents -15 countries</td>
<td>United States</td>
</tr>
</tbody>
</table>

Are We Adhering to Clinical Guidelines?

- Adherence to clinical guidelines nationwide low
- Aapro et al showed guideline adherence of only 29% in a large European observational study (n=1000)
- INSPIRE trial by Gilmore et al also showed adherence to NCCN guidelines very low in US
  - Highly emetogenic chemotherapy (HEC) : 29%
  - Moderate emetogenic chemotherapy (MEC): 73%

Key Updates in MASCC/ESMO Guidelines

- Anthracycline + cyclophosphamide (AC) = high risk
- Inclusion of NEPA and rolapitant as NK₁ options
- High emetic risk non-AC regimen and AC
  - Acute CINV : 3 drug regimen (5HT₃RA + NK₁RA + DEX)
  - Delayed CINV (Non AC) : Above + DEX on days 2-4
  - Delayed CINV (AC): No DEX if long acting NK₁RA used
- Olanzapine may be considered with a 5HT₃RA + DEX
- Carboplatin based regimen: 5HT₃RA + NK₁RA + DEX
  - No need for delayed CINV prophylaxis with DEX

http://www.mascc.org/assets/GuidelinesTools/mascc_antiemetics
Key Updates in NCCN Guidelines

- Updated yearly and periodically
- Anthracycline + cyclophosphamide (AC) = high risk
- Inclusion of NEPA and rolapitant as NK1 options
- Olanzapine containing regimen added as option for high and moderate emetic risk
  - Acute (day 1): Olanzapine + palonosetron + DEX 20mg
  - Delayed (day 2-4): Olanzapine 10mg daily

Key Updates in ASCO Guidelines

- Update to 2011 guidelines
  - Inclusion of netupitant/palonosetron as option for patients receiving high emetic risk regimens
  - Anthracycline + cyclophosphamide (AC) = HEC
  - Palonosetron is preferred SHTRA in moderate emetic risk regimens

Guideline Recommendations: High Risk

<table>
<thead>
<tr>
<th></th>
<th>ESMO/MASSC</th>
<th>NCCN</th>
<th>ASCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute CINV: Day 1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 drug combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK1 + SHT3 + Dexamethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed CINV: Day 2-4</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Dexamethasone 8mg PO/IV daily</td>
<td></td>
<td></td>
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</tbody>
</table>

Guideline Recommendations: Moderate Risk

<table>
<thead>
<tr>
<th></th>
<th>ESMO/MASSC</th>
<th>NCCN</th>
<th>ASCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute CINV: Day 1</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2 drug combination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NK1 + SHT3 + Dexamethasone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Delayed CINV: Day 2-3</td>
<td>No</td>
<td>Consider</td>
<td>No</td>
</tr>
<tr>
<td>NK1 Receptor Antagonist</td>
<td>Palonosetron</td>
<td>May consider</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>Palonosetron</td>
<td>May consider</td>
<td></td>
</tr>
<tr>
<td>Dexamethasone 8mg PO/IV daily</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Guideline Recommendations: Low & Minimal Risk

<table>
<thead>
<tr>
<th></th>
<th>MASSC/ESMO</th>
<th>NCCN</th>
<th>ASCO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>Single agent: SHT3 or dexamethasone or dopamine antagonist</td>
<td>Single agent: SHT3 or dexamethasone or dopamine antagonist</td>
<td>Single agent: Dexamethasone 8mg PO</td>
</tr>
<tr>
<td>Minimal Risk</td>
<td>No routine prophylaxis</td>
<td>No routine prophylaxis</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

Poll Question

1. BJ is a 45 y/o newly diagnosed female with breast cancer who presents to your clinic for her 1st cycle of AC. Which of the following is appropriate for CINV prophylaxis on day 1 of chemotherapy?
   A. Netupitant/ Palonosetron 300-0.5mg + Dexamethasone 12mg
   B. Olanzapine 10mg + Palonosetron IV 0.25mg + Dexamethasone 20mg
   C. Rolapitant 180mg PO + palonosetron IV 0.25mg + Dexamethasone 12mg
   D. Olanzapine 10mg + Aloxi IV 0.25mg + Fosaprepitant 150mg IV + Dexamethasone 12mg
   E. All of the above
Conclusion

- CINV is one of the most feared complications of chemotherapy having a serious impact on patients
- CINV can be prevented and pharmacists have a huge role to ensure patients receive appropriate antiemetic regimens
- Institutions should incorporate evidence and practice based guidelines into daily practice to optimize patient care

Updates in the Management of Chemotherapy-induced Nausea and Vomiting (CINV)

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