Updates in Chemotherapy-Induced Nausea and Vomiting (CINV) – 2017

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AUGUST 5, 2017
Objectives

• Review risk factors for developing CINV
• Discuss newly-approved therapies for CINV, including granisetron subcutaneous injection and rolapitant, and review data for olanzapine in setting of prevention and treatment of CINV
• Explore other new updates to national guidelines for CINV
Updates to be covered

• New formulation of granisetron
• Newest NK-1 antagonist: rolapitant
• Olanzapine for treatment and prevention of CINV: then and now
• Change in emetogenicity of carboplatin
• Change in definition of “AC”
• Brief note about steroids for CINV
Abbreviations!

- HEC: highly emetogenic chemo
- MEC: moderately emetogenic chemo
- LEC: low emetogenic chemo
- AC: regimens containing an anthracycline and cyclophosphamide
- CIS: cisplatin
- CR: complete response (no emesis, no use of rescue meds)
- CINV: chemo-induced nausea/vomiting
- aCINV: acute CINV
- dCINV: delayed CINV
- bCINV: breakthrough CINV
- APR: aprepitant
- ROL: rolapitant
- 5HT\textsubscript{3} RA: serotonin receptor antagonist
- GRAN: granisetron extended-release injection
- GRAN5: 5 mg subQ
- GRAN10: 10 mg subQ
- PALO: palonosetron
- FOS: fosaprepitant
- NK1 RA: NK1 receptor antagonist
- OND: ondansetron
- OLZ: olanzapine
- MET: metoclopramide
- AUC: area under the curve
- DEX: dexamethasone
- aCINV: anticipatory CINV
- AE: adverse effects
- NEPA: netupitant/palonosetron
Pathophysiology of CINV

Types of CINV

• **Acute – onset:**
  – Within a few minutes to several hours
  – Peak intensity after 5 – 6 hours

• **Delayed – onset:**
  – Develops >24 hours
  – Peak intensity at 48 – 72 hours; may last 6 – 7 days!

• **Anticipatory:**
  – “Conditioned response” often due to prior negative experience

• **Breakthrough:**
  – Occurs despite antiemetic prophylaxis and/or rescue
  – **Refractory:**
    • Occurs during subsequent cycles when above not effective in earlier cycles

NCCN guidelines: v.2.2017
Risk factors for CINV – patient related

- Female gender
- No history of alcohol abuse
- History of morning- or motion- sickness
- Age (<50 years)
- Prior history of CINV
- Anxiety
- Tumor location and/or burden
- Co-morbid conditions
- Concomitant medications

NCCN guidelines: v.2.2017
Risk factors for CINV – anatomic

- Partial or complete bowel obstruction
- Malignant ascites
- Vestibular dysfunction; brain metastases
- Electrolyte imbalances; uremia
- Gastroparesis
  - Due to tumor location, chemo (vincristine, etc)
- Excessive secretions
  - Head and neck cancers

NCCN guidelines: v.2.2017
Risk factors for CINV – treatment related

• Emetogenicity of chemotherapy agent(s):
  – **High**: emesis in >90% of patients
  – **Moderate**: emesis in 30-90% of patients
  – **Low**: emesis in 10-30% of patients
  – **Minimal**: emesis in <10% of patients

• Dose – level of emetogenicity may vary

• Route and schedule of administration

• Drug administration (bolus vs. infusion)

NCCN guidelines: v.2.2017
Audience Response Question #1

Which of the following patients is NOT at an increased risk for experiencing CINV?

A) A 40-year old patient with metastatic ovarian cancer and malignant ascites

B) A 75-year old male with lung cancer and history of heavy alcohol consumption

C) A 60-year old male with head and neck cancer receiving therapy with cisplatin and XRT

D) A 35 year old female with breast cancer and a history of refractory morning sickness during her two prior pregnancies
Granisetron

• Serotonin 5HT$_3$ RA

• Available in many formulations
  – Oral tablets (Kytril®)
  – Intravenous (Kytril®)
  – Transdermal patch (Sancuso®)
    • FDA approval: prevention of N/V for MEC and HEC
  – Extended-release subQ injection (Sustol®)
    • FDA approval: prevention of aCINV and dCINV with MEC or AC regimens
GRAN (Sustol®) injection

• Approved in combination with other antiemetics in adults for prevention of acute and delayed CINV
  – MEC or AC regimens

• Extended-release formulation, polymer-based drug delivery
  – Dose: 10 mg pre-chemo on Day 1; no more than weekly
  – Must be at room temperature prior to administration

• Subcutaneous administration only
  – Not interchangeable with IV formulation
  – Administer in back of upper arm or abdomen
  – Slow sustained administration over 20-30 seconds

NCCN guidelines: v.2.2017
Granisetron (Sustol®) prescribing information. 11/2016.
GRAN (Sustol®) injection

- Detected in plasma for 7 days post-dose
- Plasma protein binding ~65%
- Metabolized by CYP1A1 and CYP3A4
- Clearance by hepatic metabolism
- Only 12% eliminated unchanged in urine
  - Rest as metabolites
- Dose adjustment for renal impairment
  - CrCl 30-59 ml/min: every 14 day administration
- Doesn’t significantly prolong QTc

NCCN guidelines: v.2.2017
Granisetron (Sustol®) prescribing information. 11/2016.
GRAN vs. PALO for CINV

- Phase III, randomized, double-blind
- Prevention of aCINV and dCINV
  - After MEC or HEC
- Noninferiority of GRAN vs PALO
  - GRAN 5 mg, 10 mg doses SubQ; PALO 0.25 mg IV
- Primary efficacy endpoint
  - % CR in acute (0-24h) and delayed (24-120h) phases
- Secondary endpoints
  - % CR over entire (0-120h) period
  - Safety

Support Care Cancer 2015;23:723-32.
GRAN vs. PALO – results

• Both doses GRAN noninferior to PALO in preventing aCINV after MEC and HEC:
  – CR (MEC): 74.8% GRAN5, 76.9% GRAN10, 75% PALO
  – CR (HEC): 77.7% GRAN5, 81.3% GRAN10, 80.7% PALO

• GRAN10 noninferior to PALO for preventing dCINV
  – In patients receiving MEC*
    – GRAN10 58.5%, PALO 57.2%

• Most common side effects injection site reaction, constipation

*At the time study designed, PALO did not have established benefit in dCINV with HEC!

Support Care Cancer 2015;23:723-32.
GRAN vs. PALO – considerations

• No NK-1 RA included in HEC regimen
  – Now is standard of care; can’t compare to more recent data
• Could not compare GRAN and PALO in HEC
• GRAN and PALO both long-acting (big plus!)
• Regimens studied reclassified by ASCO 2011:
  – Study HEC regimen: carboplatin/taxane → now MEC
  – Study MEC regimen: AC → now HEC
  – May explain higher rates of control in HEC!

Support Care Cancer 2015;23:723-32.
MAGIC trial

- GRAN vs. OND for prevention of CINV with HEC
  - Cycle 1 of single day therapy with HEC
  - Regimens
    - GRAN 10 mg or OND 0.15 mg/kg IV
    - FOS 150 mg IV and DEX 12 mg IV
      - DEX 8 mg PO D2; DEX 8 mg PO BID D3-4
- Primary endpoint: delayed-phase CR (24-120h)
- Secondary endpoints:
  - Overall CR (at 0-120h), rate of no emetic episodes
  - Overall complete control (CC)

MAGIC trial – results

MAGIC trial - considerations

• In past, IV and PO granisetron and OND have not demonstrated efficacy against dCINV
  – But, SubQ GRAN provides sustained therapeutic concentrations of drug for ≥5 days!
    • Clinically meaningful to those receiving HEC

• GRAN vs. OND: a fair comparison?

• Majority (80%) subjects were women
  – Lower than expected CR rates?

• Short follow up time
Rolapitant (Varubi®): new NK1 RA

- FDA approval: prevention of dCINV in combination with DEX and 5HT₃ RA for emetogenic chemotherapy, includes HEC
- Dose 180 mg PO, 1 – 2 hours prior to chemo – 90 mg tablets
- DEX dose does not need to be adjusted
- Strong CYP3A4 inducers decreases plasma concentrations, should be avoided
Rolapitant (Varubi®): new NK1 RA

- Detected in plasma within 30 minutes; peak plasma concentration 4h after single oral dose
- Highly protein bound (>99%)
- Terminal half-life approximately 7 days
- Metabolized primarily by CYP3A4 to active major metabolite
- Elimination primarily biliary/hepatic
- Does not significantly affect QTc

Rolapitant (Varubi®) prescribing information. 9/2015.
# Comparison of available NK1 RA

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>Route</th>
<th>T 1/2</th>
<th>Dose Adjust for Renal/ Hepatic?</th>
<th>Affects DEX metabolism?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aprepitant</td>
<td>D1: 125 mg</td>
<td>PO</td>
<td>9-13 h</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td></td>
<td>D2,3: 80 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fosaprepitant</td>
<td>150 mg</td>
<td>IV</td>
<td>~11 h</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>Netupitant/</td>
<td>300 mg/0.5 mg</td>
<td>PO</td>
<td>NE: 80-109 h</td>
<td>Avoid in ESRD, severe liver</td>
<td>YES</td>
</tr>
<tr>
<td>Palonosetron*</td>
<td></td>
<td></td>
<td>PA: 48-67 h</td>
<td>disease</td>
<td></td>
</tr>
<tr>
<td>Rolapitant</td>
<td>180 mg</td>
<td>PO</td>
<td>~7 days</td>
<td>Not studied in ESRD; avoid in</td>
<td>NO</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>severe liver disease</td>
<td></td>
</tr>
</tbody>
</table>

Sources: respective package inserts
ROL for preventing CINV with carboplatin

- Phase III, randomized, double-blind
- ROL vs. placebo, with GRAN plus DEX

Notable endpoints: CR in overall, acute, and delayed phases

*Cancer* 2016;122:2418-25
ROL for preventing CINV - results

- Overall incidence of AEs similar between groups
- No patients with treatment – related serious AEs

*Cancer* 2016;122:2418-25
Audience Response Question #2

Which of the following is FALSE about the new GRAN subcutaneous formulation?

A) It is approved in combination with other agents for treatment of both aCINV and dCINV
B) It is interchangeable with the IV formulation
C) Administration should be no more than every 14 days in patients with CrCl 30-59 ml/min
D) GRAN was found to be noninferior to PALO in preventing aCINV after MEC and HEC
Olanzapine (OLZ): “Then and Now”

- Second generation atypical antipsychotic
- Not FDA-approved for CINV
- Only antiemetic that blocks many receptors
- Half-life range is broad: 21-54 hours
- Metabolized by CYP1A2, CYP2D6
  - But is NOT an inhibitor
- Previously studied for treatment of CINV
- Now being used in prevention as well!
Receptors targeted by OLZ

Dopaminergic: D1, D2, D3, D4
Serotonergic: 5HT$_{2A}$, 5HT$_{2C}$, 5HT$_{3}$, 5HT$_{6}$
Adrenergic: alpha-1
Histaminergic: H1
Muscarinic: M1, M2, M3, M4

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OLZ for CINV prevention ("Then")

- Patients receiving HEC: Cisplatin $\geq 70 \text{ mg/m}^2$ or AC
- Randomized to OLZ- or APR- containing 3-drug regimen

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>Day 1</th>
<th>Days 2 – 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>“OPD”</td>
<td>124</td>
<td>OLZ 10 mg PO</td>
<td>OLZ 10 mg PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PALO 0.25 mg IV</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEX 20 mg IV</td>
<td></td>
</tr>
<tr>
<td>“APD”</td>
<td>123</td>
<td>APR 125 mg PO</td>
<td>APR 80 mg PO D2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PALO 0.25 mg IV</td>
<td>D2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DEX 12 mg IV</td>
<td>DEX 4 mg PO D2-4</td>
</tr>
</tbody>
</table>

- Primary endpoint: CR at 0-120 hours
- Secondary endpoints:
  - CR in acute (0-24h) and delayed (25-120h)
  - No nausea in each phase

OLZ for CINV prevention – results

• Primary endpoint (CR in overall phase):
  – No significant difference (p>0.05)

• Secondary endpoint (CR in acute, delayed phases):
  – No significant difference (p>0.05)

• Secondary endpoint (nausea control):
  – OPD had higher nausea control rates in delayed and overall phases when compared to APD (p<0.01)
  – No difference in acute phase (p>0.05)
OLZ vs. MET for bCINV (“Then”)

- Patients scheduled to receive HEC
  - \( \geq 70 \, \text{mg/m}^2 \) cisplatin or AC
- All received appropriate 3-drug prophylaxis
  - Day 1: FOS 150 mg IV, PALO 0.25 mg IV, DEX 12 mg IV
  - Days 2-4: DEX 4 mg PO BID
- Breakthrough medication within 30 minutes of emesis and/or significant nausea
  - OLZ 10 mg PO daily x 3 days or MET 10 mg PO Q8h x 3 days
- Primary endpoint: no emetic episodes in 72-h
- Secondary endpoint: no nausea in 72-h

## OLZ vs. MET for bCINV – results

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>OLZ group (% patients)</th>
<th>MET group (% patients)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No emesis at 72 hours</td>
<td>68</td>
<td>23</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>No nausea at 72 hours</td>
<td>70</td>
<td>31</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

- Adverse effects reported with OLZ
  - fatigue, drowsiness, dry mouth

OLZ for prevention of CINV (“Now”)

- Phase III, randomized, placebo – controlled
- Cisplatin ≥ 70 mg/m² or equivalent of AC
- Primary endpoint: nausea prevention
- Secondary endpoint: CR

<table>
<thead>
<tr>
<th>Day 1</th>
<th>Days 2 – 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR 125 mg PO or FOS 150 mg IV x 1</td>
<td>APR 80mg PO Days 2-3 (if on D1)</td>
</tr>
<tr>
<td>5-HT₃ receptor antagonist</td>
<td>DEX 8 mg PO/IV Days 2-4</td>
</tr>
<tr>
<td>DEX 12 mg PO/IV</td>
<td>OLZ 10 mg PO Days 2-4</td>
</tr>
<tr>
<td><strong>OLZ 10 mg PO x 1 or placebo</strong></td>
<td><strong>OLZ 10 mg PO Days 2-4 or placebo</strong></td>
</tr>
</tbody>
</table>

NEJM 2016;375(2):134-42.
### OLZ for prevention of CINV - results

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>OLZ (%)</th>
<th>Placebo (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No nausea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time point:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 24 h</td>
<td>74</td>
<td>45</td>
<td>0.002</td>
</tr>
<tr>
<td>25 – 120 h</td>
<td>42</td>
<td>25</td>
<td>0.002</td>
</tr>
<tr>
<td>0 – 120 h</td>
<td>37</td>
<td>22</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>CR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time point:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – 24 h</td>
<td>86</td>
<td>65</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25 – 120 h</td>
<td>67</td>
<td>52</td>
<td>0.007</td>
</tr>
<tr>
<td>0 – 120 h</td>
<td>64</td>
<td>41</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*NEJM* 2016;375(2):134-42.
Sedation with OLZ for prevention of CINV

NEJM 2016;375(2):134-42.
Olanzapine (OLZ) dosing

- Phase II randomized, double blind study
- Highly emetogenic chemotherapy
  - Cisplatin ≥ 50 mg/m²
- Four-drug combination
  - Aprepitant, dexamethasone, palonosetron
  - *OLZ 5 or 10 mg daily after dinner, days 1-4*
- Primary endpoint: complete response (CR)
  - No emesis or rescue meds in delayed phase
    - 24 – 120 hours post-chemo

*J Clin Oncol* 2016;34 Abstract 10111
## Olanzapine dosing – results

<table>
<thead>
<tr>
<th></th>
<th>CR in delayed phase (%)</th>
<th>80% confidence interval</th>
<th>p – value</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Historical control”</td>
<td>≤ 65</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>OLZ 5 mg</td>
<td>85.7</td>
<td>79.2 – 90.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>OLZ 10 mg</td>
<td>77.6</td>
<td>70.3 – 83.8</td>
<td>0.01</td>
</tr>
</tbody>
</table>

- Most common adverse effect: somnolence
  - 45.5% with 5 mg dose; 53.3% with 10 mg dose
- Other considerations

*J Clin Oncol* 2016;34 Abstract 10111
Updated carboplatin stratification

- Carboplatin previously categorized as having moderate emetogenic risk at all dosing AUCs
- New updates to NCCN guidelines stratify:

<table>
<thead>
<tr>
<th>Dose (AUC)</th>
<th>Old</th>
<th>New</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 4</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td>≥ 4</td>
<td>Moderate</td>
<td><strong>HIGH</strong></td>
</tr>
</tbody>
</table>

*NCCN guidelines: v.2.2017*
Updated definition of AC combination

- Highly emetogenic chemotherapy

- Previously:
  - “AC” designated as the specific regimen used to treat breast cancer
    - Doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m²

- Now:
  - “AC” is defined as any chemo regimen that contains both an anthracycline and cyclophosphamide
    - No longer just refers to common breast cancer regimen

NCCN guidelines: v.2.2017
A quick note on steroids for CINV

- Steroids mainstay for CINV in HEC, MEC, also LEC
- Immunotherapy has become hot topic in treatment of both early- and late stage cancer
- Use of steroids as an antiemetic **not** recommended in setting of immunotherapy or cellular therapy
  - May decrease efficacy of therapy by blunting patients’ immune response to therapy
  - Non-steroid alternatives necessary in this setting
  - Often used for treatment of immune effects of new agents

NCCN guidelines: v.2.2017
<table>
<thead>
<tr>
<th>HEC Regimen</th>
<th>Day 1</th>
<th>Days 2, 3, 4</th>
</tr>
</thead>
</table>
| **A**       | APR 125 mg PO x 1  
5HT<sub>3</sub> RA^  
DEX 12 mg x 1 | APR 80 mg PO D2,3  
DEX 8 mg D2-4 |
| **B**       | FOS 150 mg IV x 1  
5HT<sub>3</sub> RA^  
DEX 12 mg x 1 | DEX 8 mg D2, then  
DEX 8 mg BID D3,4 |
| **C**       | **ROL 180 mg PO x 1**  
5HT<sub>3</sub> RA^  
DEX 12 mg x 1 | DEX 8 mg BID D2-4 |
| **D**       | NEPA 300 mg/ 0.5 mg PO x 1  
DEX 12 mg x 1 | DEX 8 mg daily D2-4 |
| **E**       | **OLZ 10 mg PO x 1**  
PALO 0.25 mg IV x 1  
DEX 20 mg IV x 1 | **OLZ 10 mg PO D2-4** |
| **F**       | APR 125 mg PO x 1 or FOS 150 mg IV x 1  
5HT<sub>3</sub> RA^  
DEX 12 mg x 1  
**OLZ 10 mg PO x 1** | APR 80 mg PO D2,3 (if APR D1)  
DEX 8 mg daily D2-4  
**OLZ 10 mg PO D2-4** |

NCCN guidelines: v.2.2017

^Includes new GRAN subQ injection
<table>
<thead>
<tr>
<th>MEC Regimen</th>
<th>Day 1</th>
<th>Days 2 and 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>G</td>
<td>5HT₃ RA(^\wedge) (PALO or GRAN SQ preferred) DEX 12 mg x 1</td>
<td>DEX 8 mg daily D2,3 or 5HT₃ RA monotherapy D2,3*</td>
</tr>
<tr>
<td>H</td>
<td>APR 125 mg PO x 1 5HT₃ RA(^\wedge) DEX 12 mg x 1</td>
<td>APR 80 mg PO D2,3 ± DEX 8 mg daily D2,3</td>
</tr>
<tr>
<td>I</td>
<td>FOS 150 mg IV x 1 5HT₃ RA(^\wedge) DEX 12 mg x 1</td>
<td>DEX 8 mg daily D2,3</td>
</tr>
<tr>
<td>J</td>
<td><strong>ROL 180 mg PO x 1</strong> 5HT₃ RA(^\wedge) DEX 12 mg x 1</td>
<td>DEX 8 mg daily D2,3</td>
</tr>
<tr>
<td>K</td>
<td>NEPA 300 mg/ 0.5 mg PO x 1 Dex 12 mg x 1</td>
<td>DEX 8 mg daily D2,3</td>
</tr>
<tr>
<td>L</td>
<td><strong>OLZ 10 mg PO x 1</strong> PALO 0.25 mg IV x 1 DEX 20 mg IV x 1</td>
<td><strong>OLZ 10 mg PO daily D2,3</strong></td>
</tr>
</tbody>
</table>

\(^\wedge\)Includes new GRAN subQ injection

NCCN guidelines: v.2.2017
Audience Response Question #3

True or False?: In the updated NCCN guidelines, the highly emetogenic chemotherapy regimen listed as “AC” now includes any combination of an anthracycline and cyclophosphamide (not just the AC known in breast cancer)

A) True
B) False
C) Stop talking, I need a caffeine break
Summary

• There continues to be many updates for treatment of CINV
• Long-acting granisetron injection an option for use in HEC and MEC
• Rolapitant, the new NK1 RA, is long-acting and does not affect dexamethasone dosing
• Olanzapine is becoming a mainstay of therapy for both prevention and treatment of CINV
Updates in Chemotherapy-Induced Nausea and Vomiting (CINV) – 2017

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