Recent advances in the prevention of chemotherapy induced nausea and vomiting

Snežana Bošnjak
@bosnjaksupport
Clinical developments: CINV

- New insights into the pathophysiology of CINV
- Classification of antineoplastic agents according to their emetogenicity
- Identification of risk factors for CINV
- Recognition of anticipatory, acute and delayed CINV
- Development of selective 5HT3 and NK1 RA
- Anti-emetic guidelines
Antiemetic agents

- 5HT3 RA ("setrons"): OND, GRA, PALO
- NK1 RA: APR, fosAPR, netupitant, rolapitant
- Corticosteroids: DEX
- Dopamine RA: metoclopramide, haloperidol
- Olanzapine
Olanzapine

- Atypical antipsychotic
- Broad spectrum of activity against:
  - Dopamine (D1, D2, D3, and D4)
  - Serotonin (5HT2A, 5HT2C, 5HT3, 5HT6)
  - Catecholamines (α1 adrenergic)
  - Histamine (H1)
  - Acetylcholine (m1-m4)

Bosnjak SM, MASCC / ISOO 2014
Current guidelines: olanzapine

NOT included
• MASCe/ ESMO (2013)

Included (ASCO, 2011)
• Consider adding OLAN: CINV despite optimal prophylaxis

Recommended (NCCN, 2014)
• OPD as an alternative to APD (HEC, MEC)
• Olanzapine for breakthrough emesis

Ongoing trial: Antiemetic Tx w/ or w/o Olan: CINV (HEC) NCT02116530
NEPA : NEtupitant + PAlonosetron

NEPA: the first oral fixed-dose combination agent

Two antiemetics in a single capsule: once per cycle schedule

Netupitant: a new NK1 RA

Potent and highly selective NK1 RA with a long half-life (96h)

Palonosetron: pharmacologically distinct & clinically superior 5-HT₃ RA

- A longer plasma half-life (>40 h), inhibition of receptor function and higher binding affinity
- The enhanced clinical efficacy and better control of emesis esp. delayed emesis
- Inhibition of intracellular ‘crosstalk’ between 5-HT₃ and NK1 receptors: ability to work synergistically with netupitant
Efficacy and safety of NEPA, an oral combination of netupitant and palonosetron, for prevention of CINV following highly emetogenic chemotherapy

http://annonc.oxfordjournals.org/
**Study Treatments**

Phase 2, dose-ranging, double-blind, pivotal study

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Days 2 and 3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Palo</strong></td>
<td>PALO 0.5 mg + DEX 20 mg + Placebo</td>
<td>DEX 8 mg BID</td>
<td>DEX 8 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEPA&lt;sub&gt;100&lt;/sub&gt;</strong></td>
<td>PALO 0.5 mg + NETU 100 mg + DEX 12 mg</td>
<td>DEX 4 mg BID</td>
<td>DEX 4 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEPA&lt;sub&gt;200&lt;/sub&gt;</strong></td>
<td>PALO 0.5 mg + NETU 200 mg + DEX 12 mg</td>
<td>DEX 4 mg BID</td>
<td>DEX 4 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>NEPA&lt;sub&gt;300&lt;/sub&gt;</strong></td>
<td>PALO 0.5 mg + NETU 300 mg + DEX 12 mg</td>
<td>DEX 4 mg BID</td>
<td>DEX 4 mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>APR + OND (exploratory)</strong></td>
<td>OND 32 mg + APR 125 mg + DEX 12 mg</td>
<td>APR 80 mg + DEX 4 mg BID</td>
<td>DEX 4 mg BID</td>
</tr>
</tbody>
</table>

N=694 Randomized 1:1

DEX, dexamethasone; BID, twice daily; NETU, PALO and APR were administered orally 60 min prior to cisplatin on Day 1. DEX was administered orally 30 min prior to cisplatin on Day 1. OND was administered as 50 mL intravenous infusion of at least 15 min duration prior to cisplatin on Day 1.

Efficacy: HEC
Complete Response (No Emesis, No Rescue)

PALO = palonosetron, NEPA = fixed dose combination of PALO + netupitant (NETU), DEX = dexamethasone.

A randomized Phase 3 study evaluating the efficacy and safety of NEPA, a fixed combination of netupitant and palonosetron, for prevention of chemotherapy-induced nausea and vomiting following moderately emetogenic chemotherapy

Ann Oncol 2014; doi: 10.1093/annonc/mdu101
http://annonc.oxfordjournals.org/
### Study Treatments

Multinational, phase 3 study in patients receiving AC-MEC

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>PALO</td>
<td>PALO 0.5 mg + DEX 20 mg</td>
</tr>
<tr>
<td>NEPA</td>
<td>PALO 0.5 mg + NETU 300 mg + DEX 12 mg</td>
</tr>
</tbody>
</table>

N=1455
Randomized 1:1

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

Efficacy: AC-MEC
Complete response (No emesis, No rescue)

Efficacy: AC-MEC
Overall Complete Response (0-120h): Multiple Cycles

Quality of life assessment

FLIE: No impact on daily living, nausea and vomiting

A Phase 3 study evaluating the safety and efficacy of NEPA, a fixed combination of netupitant and palonosetron, for prevention of CINV over repeated cycles of chemotherapy.

**Study Treatments**

Phase 3 safety study: multiple cycles, HEC & non-AC MEC

<table>
<thead>
<tr>
<th>Group</th>
<th>Day 1</th>
<th>Day 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR+ PALO</td>
<td>APR 125 mg + PALO 0.5 mg</td>
<td>APR 80 mg</td>
</tr>
<tr>
<td>NEPA₃₀₀</td>
<td>NETU 300 mg + PALO 0.5 mg</td>
<td></td>
</tr>
</tbody>
</table>

PLUS DEX:
- HEC: Day 1: 12 mg, Days 2–8 mg;
- MEC: D1: 12 mg
The majority of treatment-emergent adverse events were of mild/moderate intensity

Table 4: Overview of adverse events

<table>
<thead>
<tr>
<th></th>
<th>NEPA (N = 308)</th>
<th>APR + PALO (N = 104)</th>
<th>NEPA (N = 308)</th>
<th>APR + PALO (N = 104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
<td>Entire Multiple Cycle Study Period*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any TEAE †</td>
<td>199 (64.6)</td>
<td>64 (61.5)</td>
<td>265 (86.0)</td>
<td>95 (91.3)</td>
</tr>
<tr>
<td>Treatment-related adverse event‡</td>
<td>16 (5.2)</td>
<td>3 (2.9)</td>
<td>31 (10.1)</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Severe treatment-related adverse event</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Serious treatment-related adverse event</td>
<td>1 (0.3)</td>
<td>0</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Treatment-related adverse event leading to discontinuation</td>
<td>1 (0.3)</td>
<td>0</td>
<td>1 (0.3)</td>
<td>0</td>
</tr>
<tr>
<td>Total deaths (all unrelated to study drug)</td>
<td>7 (2.3)</td>
<td>0</td>
<td>16 (5.2)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

## Safety analysis

The most common **treatment-related** adverse events

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>NEPA (N=308)</th>
<th>APR + PALO (N=104)</th>
<th>NEPA (N=308)</th>
<th>APR + PALO (N=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cycle 1</td>
<td>Entire multiple cycle study period*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>7 (2.3)</td>
<td>0</td>
<td>11 (3.6)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>1 (1.0)</td>
<td>1 (0.3)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Eructation</td>
<td>1 (0.3)</td>
<td>1 (1.0)</td>
<td>1 (0.3)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (1.0)</td>
<td>1 (1.0)</td>
<td>3 (1.0)</td>
<td>1 (1.0)</td>
</tr>
</tbody>
</table>

Safety population; *includes cycle 1 through all cycles
Cardiac safety analysis

There were no cardiac safety concerns based on cardiac AEs and ECGs

- Changes from baseline (12-lead ECGs, at 5 & 24 hours post-dose): similar between the groups

- Any QTc interval prolongation: transient and returning to pre-dose measurements within 120 hours post-dose across all cycles

- The percentage of patients with ECG abnormalities: comparable throughout the study

- High post-dose troponin values: in 7 (2.3%) NEPA-treated patients and 3 (2.9%) APR-treated patients

- Mean LVEF: comparable at screening and at the end of the study with small changes in both groups

Efficacy: HEC & non-AC MEC
Overall (0-120h) Complete Response: multiple cycles

The efficacy of NEPA + DEX on nausea control was maintained over multiple (4-6) cycles.

No Significant Nausea Rates
Overall phase (0-120 hr): HEC and non-AC MEC

<table>
<thead>
<tr>
<th>Cycle</th>
<th>NEPA + DEX</th>
<th>APR + PALO + DEX</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>84.1</td>
<td>84.1</td>
</tr>
<tr>
<td>2</td>
<td>86.8</td>
<td>86.8</td>
</tr>
<tr>
<td>3</td>
<td>89.6</td>
<td>83.3</td>
</tr>
<tr>
<td>4</td>
<td>91.8</td>
<td>86.4</td>
</tr>
<tr>
<td>5</td>
<td>92.3</td>
<td>82.5</td>
</tr>
<tr>
<td>6</td>
<td>90.3</td>
<td>84.1</td>
</tr>
</tbody>
</table>

NEPA+DEX N = 309
APR+PALO+DEX N = 103
Rolapitant

- Novel NK1 RA
- Long (180h) half life and ability to be given in a single dose (200 mg) per cycle
- Two Phase III Trials Find Rolapitant Effective, Well-Tolerated for Preventing CINV (HEC, MEC) (MASCC / ISOO 2014)
- Different efficacy in the different phases
TD granisetron

- Constant delivery of GRA over 5-7 days
- Similar plasma level to oral dose of 2 mg per day
- Non inferior to oral GRA in the control of CINV (multiple day chemotherapy)
- ? Alternative option to IV or oral GRA (HEC, MEC, MASCC /ISOO 2014)
Conclusion

- CINV: to be prevented and NOT tolerated by the patients
- Ongoing intensive antiemetic research