RESEARCH AND PROGRESS IN ANTIEMETICS:
Newer Results influencing Practical Aspects of Cancer Care

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CONTROLLING EMESIS WITH CHEMOTHERAPY
- New Findings which can affect Practice -

• New Agents
• New Indications
• Updated Guidelines
• New Evidence
EVIDENCE AND TARGETS*

Expression

Possible target

Expression + activation

Promising target

Expression + activation + mechanism

A major target for a clinical trial

Expression + activation + mechanism + drug

A potentially valuable therapy

NEUROTRANSMITTERS AND ANTIEMETIC PATHWAYS:
Targeting Key Pathways to Influencing Emetic Control

Dopamine / $D_2$ RAs

Histamine

Endorphins

Acetylcholine

GABA

Cannabinoids

Emetic reflex

Serotonin / 5-HT$_3$ RAs

Substance P / NK$_1$ RAs

DA = dopamine; GABA = gamma-aminobutyric acid; NK = neurokinin

RAs = receptor antagonists
NK₁ RECEPTOR ANTAGONIST AGENTS
Approved for Use as Antiemetics

Aprepitant (oral)
Fos-aprepitant (IV)
Netupitant (and NEPA)
Rolapitant

* All these agents are now FDA approved in the US, as of September 2015
APREPITANT IN PEDIATRICS 2015
- Phase III Randomized Trial (N = 302) -

- Double-blind study in children ages 6 months to 17 years receiving chemotherapy with a 5HT$_3$ receptor antagonist with or without Aprepitant
- Most patients were previously treated and received multiple days of chemotherapy
- Dexamethasone was elective and given to only 43%
- Minor metabolic differences in the youngest children
- **Results:** Double the complete response rate in the aprepitant arm (20 – 30% absolute improvement)

Kang et al. Lancet Oncology 2015
Why develop new antiemetic regimens?

Even with marked progress in effective antiemetic prophylaxis, many patients still experience emesis with chemotherapy, particularly during the delayed phase.

Reasons for emetic failure include:

- Patients are not always prescribed effective guideline-based antiemetic regimens
- Patients frequently do not adhere to delayed emesis regimens

Antiemetic guidelines result in significant improvement in the control of emesis with better resource utilization.

There is a need to enhance guideline-consistent practice and to assist patient adherence.

Evidence is needed for proper use of antiemetics in additional settings.
Background of Netupitant and “NEPA”

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

• Palonosetron is a widely used 5HT₃ RA with: a long plasma half-life, demonstrated activity both orally and IV, and an excellent safety profile
  – Palonosetron is specifically recommended in key antiemetic settings in major evidence-based guidelines
  – Unlike some older agents (especially ondansetron), palonosetron does not prolong QTc intervals

• Netupitant is a new NK₁ RA with a low side-effect profile, long plasma half-life and a long duration of receptor occupancy
**Study Design**

- Phase III, multinational, randomized, double-blind study in chemotherapy-naïve patients undergoing Anthracycline + CTX chemo

- Patients randomized to receive one of the following regimens, on Day 1 only (no continued steroids):
  - Oral NEPA + Oral DEX 12 mg
    - (NEPA = NETU 300 mg + PALO 0.50 mg)
  - Oral PALO 0.50 mg + Oral DEX 20 mg

- NEPA (netupitant + palo) or PALO were administered 60 minutes prior to chemotherapy; DEX was given orally at 30 minutes prior to chemotherapy
- No other antiemetic was given as part of either study regimen after Day 1

NEPA PHASE III TRIAL IN AC CHEMO

Complete Response Rates

Percent of patients

CR: no emesis, no rescue medication
Based on full analysis set of 1449 patients

Complete Response Rates: Overall (0-120 hr) Over 6 Cycles

<table>
<thead>
<tr>
<th>Cycle</th>
<th>NEPA</th>
<th>APR + PALO</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81%</td>
<td>76%</td>
</tr>
<tr>
<td>2</td>
<td>86%</td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td>91%</td>
<td>87%</td>
</tr>
<tr>
<td>4</td>
<td>90%</td>
<td>88%</td>
</tr>
<tr>
<td>5</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>6</td>
<td>91%</td>
<td>86%</td>
</tr>
</tbody>
</table>

Number of patients:
- NEPA: N = 309, 280, 259, 233, 156, 124
- APR + PALO: N = 103, 96, 90, 81, 57, 44

Similar results observed for both the HEC and MEC subsets. No formal statistical comparisons were performed.

Rolapitant: A new NK$_1$ Receptor Antagonist

- Background and Results -

• The metabolic route is an important differentiating factor
  • Major metabolism is *not* via CYP 3A4
  • 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
  • Clear evidence of 3-drug superiority over 2-drug regimens
  • Consistency of efficacy and safety, across trials and across the chemotherapy tested (Highly and Moderately Emetic)

Rolapitant Phase III Trial
- Clinical Efficacy in Moderately Emetic Chemotherapy -

Chemotherapy: One or more of the following: cyclophosphamide, doxorubicin, epirubicin, carboplatin, idarubicin, ifosfamide, irinotecan, daunorubicin, cytarabine.
More than 50% of patients received anthracycline + cyclophosphamide (AC) chemotherapy.
Primary endpoint = Complete Response in delayed emesis

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 NK₅RA, or
  - As the 4th drug in a combination, or
  - In a regimen in patients who have not done well on the first cycle
OLANZAPINE 4-AGENT PHASE II TRIAL - In GYN Malignancies with Cisplatin -

- 40 Patients receiving initial chemotherapy with Cisplatin > 50 mg/M2

- **Regimen**: Aprepitant + Palonosetron + Dex PLUS OLANZAPINE (5 mg po for 6 days, beginning the day before chemotherapy)

- **Results**:

<table>
<thead>
<tr>
<th></th>
<th>ACUTE</th>
<th>DELAYED</th>
<th>OVERALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>No vomiting + no rescue + no 'significant' nausea</td>
<td>92.5%</td>
<td>87.5%</td>
<td>82.5%</td>
</tr>
<tr>
<td>No vomiting + no rescue + no nausea</td>
<td>87.5%</td>
<td>67.5%</td>
<td>67.5%</td>
</tr>
</tbody>
</table>

- **Side Effects**: No Grade 3 or 4 Adverse Events – Increased Sedation

Reference: Abe et al. *Supportive Care in Cancer* 2015, PMID: 26130365
OLANZAPINE 4-AGENT PHASE III Alliance 221301 TRIAL
- Randomized, Double-Blind Study-

- Cisplatin $\geq 70$ mg/M$^2$ or Cyclophosphamide / Doxorubicin (600 / 60 mg/M$^2$)

- **Antiemetics**: 3 Drugs for All: 1) Aprepitant or Fos-aprepitant + 2) Dexamethasone x 3 days + 3) $5HT_3$ 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 + Olanzepine (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: Olanzapine 6%; Placebo 2%

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

Reference: Navari et al. Oral Presentation: Palliative Care in Oncology Symposium, Boston, October 9, 2015
MAKING PROGRESS IN CONTROLLING EMESIS: EFFICACY AND EFFECTIVENESS

- Acceptance that our goals must be higher
- Recognition of the magnitude of the problem
- Re-evaluation of each effective class of agents
  - The Role of Corticosteroids
  - The Choice of Serotonin Antagonist
  - The Use of NK$_1$ Antagonists
- Investigation of newer regimens
- Applying the most effective regimens as indicated
# Randomized Trial Testing Dexamethasone in Delayed Emesis: CTX / Anthra


## Day 1:
All patients: Palonosetron 0.25 mg IV + Dexamethasone 8 mg IV

## Days 2 & 3:

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DEX 4 mg orally 2x / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 151</td>
<td></td>
<td>n = 149</td>
</tr>
<tr>
<td>5 Day CR:</td>
<td>54%</td>
<td>54%</td>
</tr>
<tr>
<td>Acute:</td>
<td>70%</td>
<td>69%</td>
</tr>
<tr>
<td>Delayed:</td>
<td>62%</td>
<td>66%</td>
</tr>
</tbody>
</table>

All women: Malignant breast; med age 52. **Endpoint**: 5 Day CR – Noninferior ≤ 15%

No nausea (delayed) favored DEX (62% vs 55%); no diff in FLIE (p=0.64) or side effects.
CONTINUED NEEDS AND RESEARCH THEMES

Major Themes:

Nausea Control
Delayed Emesis
Pediatrics
Radiation Therapy
Multiple Day Treatment
Improving Adherence to Evidence-based Guidelines

Improved Knowledge for:

Chemotherapeutic Agents which are Less Studied
Oral Agents
Molecularly Targeted Agents
The benefit of the Addition of NK$_1$ Receptor Antagonists in patients receiving carboplatin:

- Results of Phase III Trials -

<table>
<thead>
<tr>
<th>Overall (0–120 hours)</th>
<th>APR + 5-HT$_3$ RA + DEX</th>
<th>5-HT$_3$ RA + DEX</th>
<th>Absolute difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No emesis rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gralla (N = 192) *</td>
<td>84%</td>
<td>70%</td>
<td>14%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Overall (0–120 hours)</th>
<th>NK$_1$ RA + 5-HT$_3$ RA + DEX</th>
<th>5-HT$_3$ RA + DEX</th>
<th>Absolute difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tanioka (N = 91) * , **</td>
<td>62%</td>
<td>52%</td>
<td>10%</td>
</tr>
<tr>
<td>Ito (N = 134) *</td>
<td>80%</td>
<td>67%</td>
<td>14%</td>
</tr>
<tr>
<td>Yahata (N = 324) * , **</td>
<td>62%</td>
<td>47%</td>
<td>15%</td>
</tr>
<tr>
<td>Hesketh (N = 401) ***</td>
<td>80%</td>
<td>65%</td>
<td>15%</td>
</tr>
</tbody>
</table>

KEY:  * = Aprepitant based; ** = GYN only; *** Rolapitant based

RISK FACTORS FOR EMESIS AND CONTROL
- Clinical Risk Factors and Personalization -

• Chemotherapy Regimen
• Gender
• Age
• Chronic Alcohol Intake History
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. Evidence-based guidelines…actually work!
   – Higher control rates and better resource utilization

5. Evidence-based guidelines address both under usage as well as over-use of antiemetics
Primary Objective:

To compare Complete Response rates over 5 Days post-chemotherapy among patients receiving:

- **Guideline consistent** Antiemetic prophylaxis (GCCP)

with those receiving:

- **Guideline inconsistent** Antiemetic prophylaxis (GICP)

Aapro et al *Ann Oncol* 2012; Gilmore et al *J Oncol Practice* 2014
## Pan European Emesis Registry ("PEER") Study: Design & Patients, Using MASCC Guidelines

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>991</td>
</tr>
<tr>
<td>Where conducted</td>
<td>8 European countries (including UK)</td>
</tr>
<tr>
<td>Percent women</td>
<td>73%</td>
</tr>
<tr>
<td>Median Age</td>
<td>57 years</td>
</tr>
<tr>
<td>Percent HEC / AC / MEC</td>
<td>19% / 47% / 34%</td>
</tr>
<tr>
<td>Percent Guideline Compliant</td>
<td>29%</td>
</tr>
<tr>
<td>Percent 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 / ODDS RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>287</td>
<td>704</td>
<td></td>
</tr>
<tr>
<td>Complete Response Rate</td>
<td>60%</td>
<td>51%</td>
<td>.008 / 1.43</td>
</tr>
<tr>
<td>No Nausea Rate (VAS &lt; 5)</td>
<td>48%</td>
<td>41%</td>
<td>.016 / 1.41</td>
</tr>
</tbody>
</table>

## U.S. Registry (“INSPIRE”) Study: Design & Patients, Using: EMRs, the MAT and NCCN Guidelines

<table>
<thead>
<tr>
<th>PARAMETER:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>1295</td>
</tr>
<tr>
<td>Where conducted</td>
<td>4 Oncology Practice Networks</td>
</tr>
<tr>
<td>Percent women</td>
<td>70%</td>
</tr>
<tr>
<td>Median Age</td>
<td>59 years</td>
</tr>
<tr>
<td>Percent HEC / AC / MEC</td>
<td>11% / 25% / 64%</td>
</tr>
<tr>
<td>Percent Guideline Compliant</td>
<td>57%</td>
</tr>
<tr>
<td>Percent Non-Compliant</td>
<td>43%</td>
</tr>
</tbody>
</table>

Gilmore et al *J Oncol Practice* 2014
U.S. Registry ("INSPIRE") Study: Results, Using: EMRs, the MAT and NCCN Guidelines

<table>
<thead>
<tr>
<th>PARAMETER:</th>
<th>GUIDELINE COMPLIANT</th>
<th>GUIDELINE NON-COMPLIANT</th>
<th>p / ODDS RATIO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>742</td>
<td>553</td>
<td></td>
</tr>
<tr>
<td>Complete Response Rate</td>
<td>53%</td>
<td>44%</td>
<td>&lt;.001 / 1.31</td>
</tr>
<tr>
<td>No Nausea Rate (VAS &lt; 25)</td>
<td>54%</td>
<td>45%</td>
<td>.001 / 1.28</td>
</tr>
</tbody>
</table>

Gilmore et al J Oncol Practice 2014
Resource Utilization (cycle 1): “PEER” Study
Using MASCC Guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GCCP (“Compliant”) (N = 287)</th>
<th>GICP (“Not Compliant”) (N = 704)</th>
<th>Total (N = 991)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit to: Primary Care Physician, or Specialist, or ER</td>
<td>14 (4.9%)</td>
<td>40 (7.7%)</td>
<td>66 (6.6%)</td>
</tr>
<tr>
<td>Hospital days</td>
<td>5 (1.7%)</td>
<td>10 (1.4%)</td>
<td>15 (1.5%)</td>
</tr>
</tbody>
</table>

**Note:** In a busy practice treating 100 patients per day, the rate with non-compliance with Antiemetic Guidelines results in 700 additional urgent visits per year.
### Overview of Guidelines for Acute Nausea and Vomiting

Bringing together NCCN / ASCO / MASCC-ESMO

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

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

** Some variance in palo recommendation: broader use in NCCN, narrower in ASCO
OVERVIEW OF GUIDELINES FOR DELAYED NAUSEA AND VOMITING BRINGING TOGETHER NCCN / ASCO / MASCC-ESMO

<table>
<thead>
<tr>
<th>EMETIC RISK GROUP</th>
<th>ANTIEMETICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>DEX + NK1** or none</td>
</tr>
<tr>
<td>Anthracyline + Cyclophosphamide (AC)</td>
<td>NK1** 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>

**NOTE**: if Netupitant, Rolapitant or Fos-aprepitant 150mg used on Day 1 – no further NK1 but, continue NK1 if apreptiant is used on Day 1

* 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!
CONTROLLING CHEMOTHERAPY-INDUCED EMESIS

5-day Complete Control:

- **1980**: 0% - 10%
- **1990**: 50% - 50%
- **2000**: 60% - 50%
- **2015**: 85% - 75%

**Cisplatin (Highly Emetic)**

**“AC” Chemotherapy**

- Added **5HT<sub>3</sub> + Steroids**
- Added **NK<sub>1**
ANTIEMETIC GUIDELINES
- Conclusions -

• Guidelines are the best tool to help:
  
  **Effectiveness = Efficacy**

• Antiemetic guidelines are effective in the clinic!
  
  • Guidelines improve Complete Control and Response
  
  • This control is associated with Improved Quality of Life
  
  • Guidelines improve resource utilization

• Strategies to improve guideline usage include:
  
  • Use of Evidence-based Peer-Reviewed Criteria
  
  • Linking the chemo/antiemetic ordering with guidelines
  
  • Proper education and economic incentives
Multiple roles for supportive care in cancer

- Reduce or eliminate associated symptoms and side-effects
- Preserve or improve quality of life
- Enhance the use of the most effective anti-cancer agents
- Positively affect survival and the quality of that survival

“...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