PREVENTION OF CHEMOTHERAPY INDUCED NAUSEA AND VOMITING IN ELDERLY CANCER PATIENTS

JØRN HERRSTEDT, M.D.
COPENHAGEN UNIVERSITY HOSPITAL
HERLEV, DENMARK
HISTORY OF ANTIEMETICS

1979  A corticosteroid is superior to placebo.
1981  High-dose metoclopramide (hd-MCP) is effective.
1984  A corticosteroid improves effect of hd-MCP.
1987  First clinical trial with a serotonin receptor antagonist (5-HT$_3$-RA).
1991  A corticosteroid improves the effect of 5-HT$_3$-RAs (HEC).
1993  A dopamine antagonist improves the effect of a 5-HT$_3$-RA.
1995  A corticosteroid improves the effect of 5-HT$_3$-RAs (MEC).
1997  First clinical trial with a neurokinin-1-receptor antagonist (NK$_1$-RA).
2003  NK$_1$-RA improves effect of 5-HT$_3$-RA plus corticosteroid (HEC).
2005  NK$_1$-RA improves effect of 5-HT$_3$-RA plus corticosteroid (MEC).

### 5-HT₃-receptor antagonists

- **Azasetron** Y-25130
- Batanopride BMY-25801
- Bemesetron MDL 72222
- Dazopride AHR-5531
- **Dolasetron** MDL 73,147EF Anzemet®
- Eusetron RG 12915
- **Granisetron** BRL 43694 Kytril®
- Itasetron DAU 6215
- Lerisetron F-0930
- **Ondansetron** GR 38032 Zofran®
- **Palonosetron** RS 25259-197 Aloxi®
- Pancopride LAS 30451
- **Ramosetron** YM060
- Renzapride BRL 24924
- **Tropisetron** ICS 205-930 Navoban®
- Zacopride AHR-111906
- Zatosetron LY 277359
Palonosetron vs Ondansetron in Patients Receiving Moderately Emetogenic Chemotherapy

Complete Response
Acute and Delayed Emesis

<table>
<thead>
<tr>
<th></th>
<th>Palonosetron</th>
<th>Ondansetron</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.25 mg</td>
<td>32 mg</td>
</tr>
<tr>
<td>(n=189)</td>
<td>(n=185)</td>
<td></td>
</tr>
<tr>
<td>Acute (0-24 h)</td>
<td>81.0%*</td>
<td>68.6%</td>
</tr>
<tr>
<td>Delayed (24-120 h)</td>
<td>74.1%*</td>
<td>55.1%</td>
</tr>
<tr>
<td>Overall (0-120 h)</td>
<td>69.3%*</td>
<td>50.3%</td>
</tr>
</tbody>
</table>

*97.5% CIs and two-sided Fisher’s exact test (significance level = 0.025) indicate a difference between palonosetron and ondansetron.

Complete Response (CR) = no emesis, no rescue medication.
**NK₁-receptor antagonists**

- CI-1021*
- CJ 11,974 Ezlopitant
- CP 99,994
- CP 122,721
- FK 888
- GR 203040
- GR 205171 Vofopitant
- GW 597599
- GW 679769 Casopitant
- HSP-117
- L-741671
- L-743310
- **L-754,030** Aprepitant Emend
- L-758,298***
- LY306740**
- NKP-608**
- RP-67580
- RPR-100893** Dapitant
- SR-140333** Nolpitantium

* Previously PD-154075; ** Not investigated as an antiemetic; *** Prodrug to L-754030
HIGH EMETIC RISK CHEMOTHERAPY (HEC)

# HEC - Aprepitant Phase III Trials

## Treatment Groups (n = 1099)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Days 2-3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>APR</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>32</td>
<td>D</td>
<td>D</td>
</tr>
<tr>
<td>D</td>
<td>12</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>A</td>
<td>125</td>
<td>8 + P</td>
<td>8 + P</td>
</tr>
<tr>
<td><strong>CONT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O</td>
<td>32</td>
<td>8 x 2</td>
<td>8 x 2</td>
</tr>
<tr>
<td>D</td>
<td>20</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>A</td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

O=ondansetron; D=dexamethasone; A=aprepitant; P=placebo

## HEC - Aprepitant Phase III Trial

### Treatment Groups (n = 489)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Days 2-3</th>
<th>Day 4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>O</td>
<td>D</td>
<td>A</td>
</tr>
<tr>
<td><strong>APR</strong></td>
<td>32</td>
<td>12</td>
<td>125</td>
</tr>
<tr>
<td><strong>CONT</strong></td>
<td>32</td>
<td>20</td>
<td>P</td>
</tr>
<tr>
<td></td>
<td><strong>P x 2</strong></td>
<td>8 x 2</td>
<td>8 x 2</td>
</tr>
</tbody>
</table>

O=ondansetron; D=dexamethasone; A=aprepitant; P=placebo

HEC Studies: Cycle 1
Primary Endpoint: Complete Response (0-120 h)

- **Hesketh**: Aprepitant Regimen 73%, Standard Regimen 52%
  - p<0.001
- **Poli-Bigelli**: Aprepitant Regimen 63%, Standard Regimen 43%
  - p<0.001
- **Schmoll**: Aprepitant Regimen 72%, Standard Regimen 61%
  - p=0.003
MODERATE EMETIC RISK
CHEMOTHERAPY (MEC)

MEC - Aprepitant Phase III Trial
Treatment Groups (n = 866)

<table>
<thead>
<tr>
<th></th>
<th>Day 1</th>
<th>Days 2-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR</td>
<td>OND: 8 mg x 2</td>
<td>OND: Placebo</td>
</tr>
<tr>
<td></td>
<td>DEX: 12 mg</td>
<td>APR: 80 mg</td>
</tr>
<tr>
<td>CONT</td>
<td>APR: 125 mg</td>
<td>Placebo:</td>
</tr>
<tr>
<td></td>
<td>Placebo:</td>
<td>Placebo:</td>
</tr>
</tbody>
</table>

OND = ondansetron p.o.
DEX = dexamethasone p.o.
APR = aprepitant p.o.
CONT = placebo-controlled arm

Anthracycline plus Cyclophosphamide

MEC Study: Cycle 1
Primary Endpoint: Complete Response (0-120 h)

Aprepitant Regimen (N=433)
Standard Regimen (N=424)

Complete Response (CR): 51% vs 42% (p=0.015)
No Vomiting: 76% vs 59% (p<0.001)
No Rescue Therapy: 59% vs 56% (p=ns)

MULTIPLE CYCLES OF MODERATE EMETIC RISK CHEMOTHERAPY (MEC)

Sustained No Vomiting Rate

Number at Risk:

<table>
<thead>
<tr>
<th>Time (Cycle) since First Chemotherapy</th>
<th>Aprepitant Regimen</th>
<th>Standard Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>432</td>
<td>424</td>
</tr>
<tr>
<td>1</td>
<td>296</td>
<td>224</td>
</tr>
<tr>
<td>2</td>
<td>258</td>
<td>168</td>
</tr>
<tr>
<td>3</td>
<td>234</td>
<td>139</td>
</tr>
</tbody>
</table>

Log-rank test, p<0.001

Aprepitant Regimen
Standard Regimen

Percentage of Patients

0 20 40 60 80

76% 70% 67% 63%

59% 48% 42% 39%
GUIDELINES ON ANTIEMETICS

MASCC
ASCO
ESMO
ASHP
NCCN
CCO
<table>
<thead>
<tr>
<th>Emetic risk group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Serotonin antagonist + dexamethasone + aprepitant</td>
</tr>
<tr>
<td>Anthracycline +</td>
<td>Serotonin antagonist + dexamethasone + aprepitant</td>
</tr>
<tr>
<td>Cyclophosphamide (AC)</td>
<td></td>
</tr>
<tr>
<td>Moderate (other than AC)</td>
<td>Serotonin antagonist + dexamethasone</td>
</tr>
<tr>
<td>Low</td>
<td>Dexamethasone</td>
</tr>
<tr>
<td>Minimal</td>
<td>No routine prophylaxis</td>
</tr>
</tbody>
</table>

The Antiemetic Subcommittee of The Multinational Association of Supportive Care in Cancer. Ann Oncol 2006;17:20-28. WWW.MASCC.ORG
# Prophylaxis of delayed nausea and vomiting

<table>
<thead>
<tr>
<th>Emetic risk group</th>
<th>Antiemetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Dexamethasone + aprepitant</td>
</tr>
<tr>
<td>Anthracycline + Cyclophosphamide (AC)</td>
<td>Aprepitant or dexamethasone</td>
</tr>
</tbody>
</table>
| Moderate (other than AC)              | Dexamethasone  
A serotonin antagonist may be used as an alternative                  |
| Low                                   | No routine prophylaxis                                                     |
| Minimal                               | No routine prophylaxis                                                     |

The Antiemetic Subcommittee of The Multinational Association of Supportive Care in Cancer.  
WWW.MASCC.ORG
WHAT ABOUT ANTIEMETIC THERAPY IN ELDERLY?
RISK FACTORS - CINV

- Emetic potential of chemotherapy
- Patients
- Antiemetic prophylaxis
RISK FACTORS - CINV

- Emetic potential of chemotherapy
  - Elderly often receive less toxic (less emetogenic) chemotherapy.

- Patients

- Antiemetic prophylaxis
PATIENTS

Efficacy Risk Factors

• Age
• Gender
• Previous chemotherapy
• Alcohol consumption
• Motion sickness
• Nausea and vomiting in pregnancy
PATIENTS
Toxicity Risk Factors

• Age?
• Variations in pharmacokinetics
  – Absorption
  – Renal function
  – Hepatic function
• Polypharmacy
  – Side effects from other medication
  – Risk of interactions
• Compliance
• Comorbidity
PHARMACOKINETICS AND PHARMACODYNAMICS

PALONOSETRON

- **Age**
  Population PK analysis and clinical safety and efficacy data did not reveal any differences between cancer patients $\geq 65$ years of age and younger patients (18-64 years). **No dose adjustment is required** for these patients.

- **Renal and hepatic function**
  Dosage adjustment is not necessary in patients with any degree of renal or hepatic impairment.
PHARMACOKINETICS AND PHARMACODYNAMICS

APREPITANT

• Age
  The pharmacokinetics of aprepitant are not significantly affected by race, gender, body weight, or age.

• Renal and hepatic function
  Dose adjustment of aprepitant is not necessary in patients with renal insufficiency or mild to moderate hepatic insufficiency.
DRUG INTERACTIONS

PALONOSETRON

- Palonosetron is not an inhibitor or an activator of CYP enzymes. Therefore the potential for clinically significant drug interactions with palonosetron appears to be low.
DRUG INTERACTIONS

APREPITANT

• The aprepitant regimen for CINV produces slight induction of CYP2C9 activity.
• Drugs with narrow therapeutic indices that are known to be metabolized by CYP2C9 may have transiently lower plasma concentrations when coadministered with aprepitant.
  – e.g. warfarin, phenytoin.
• For patients on warfarin INR should be appropriately monitored.
• Increases the bioavailability of oral steroids.
DRUG INTERACTIONS

OTHER

• Risk of interaction with SSRIs have been described.
  – Increased toxicity of paroxetine given concomitantly with ondansetron.
  – Decreased effect of ondansetron given concomitantly with fluoxetine.
• Metoclopramide decreases the effect of levodopa.
• Phenothiazines increase the sedative effect of hypnotics, antihistamines, alcohol and analgesics and enhance the effect of antihypertensives.
COMORBIDITY

- **Cardiovascular**
  - Prolongation of $QT_C$ with serotonin antagonists and droperidol.

- **Epilepsy**
  - Increased risk of convulsions with metoclopramide and prochlorperazine.

- **Diabetes**
  - Increased risk of constipation with serotonin antagonists due to autonomic neuropathy.
  - Increased risk of hyperglycemia with steroids.
CONCLUSIONS

• The risk of CINV is lower in elderly.
• Guidelines include no specific recommendations for the prophylaxis of CINV in elderly.
• No dose adjustment of aprepitant or serotonin antagonists is necessary due to decrease in
  – renal or
  – hepatic function (NB: ondansetron/apreptant).
• Due to polypharmacy the risk of interactions is higher in elderly.
• Comorbidity/Compliance should be evaluated.