

Highlights in CINV From the 2016 MASCC/ISOO Annual Meeting

A Review of Selected Presentations From the 2016 Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology Annual Meeting • June 23-25, 2016 • Adelaide, Australia

Special Reporting on:

- Rolapitant for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients With Breast Cancer
- Rolapitant for Control of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients With Lung Cancer
- Quality of Life, Efficacy and Patient-Reported Outcome With NEPA as CINV Prophylaxis in Highly or Moderately Emetogenic Chemotherapy
- Olanzapine for the Prophylaxis and Rescue of Chemotherapy-Induced Nausea and Vomiting (CINV): A Retrospective Study
- Rolapitant for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients Aged <65 Versus ≥65 Years
- A Single-Dose Bioequivalence Study of Rolapitant Following Oral and Intravenous Administration in Healthy Volunteers
- No Signals of Increased Toxicity After Concomitant Administration of NEPA With Etoposide or Docetaxel: Pooled Safety Data From 4 Pivotal Studies
- Phase II Study of Palonosetron, Aprepitant, Dexamethasone and Olanzapine for the Prevention of Cisplatin-Based Chemotherapy-Induced Nausea and Vomiting in Patients With Thoracic Malignancy
- Nausea as a Symptom Cluster

PLUS Meeting Abstract Summaries

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Indication and Important Safety Information for VARUBI® (rolapitant)

Indication

- VARUBI, in combination with other antiemetic agents, is indicated in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy

Contraindication

- VARUBI is contraindicated in patients receiving thioridazine, a CYP2D6 substrate. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and Torsades de Pointes

Warnings and precautions

Interaction with CYP2D6 substrates with a narrow therapeutic index

- The inhibitory effect of VARUBI on CYP2D6 lasts for at least 7 days and may last longer after administration of a single dose of VARUBI

- Avoid use of VARUBI in patients who are receiving pimozone, a CYP2D6 substrate. An increase in plasma concentrations of pimozone may result in QT prolongation

- Monitor for adverse reactions if concomitant use of VARUBI and other CYP2D6 substrates with a narrow therapeutic index cannot be avoided

Adverse reactions

- In patients receiving cisplatin-based highly emetogenic chemotherapy in cycle 1, the most common adverse reactions reported at an incidence of $\geq 5\%$ and a frequency greater than control were neutropenia (9% VARUBI vs 8% control) and hiccups (5% vs 4%)

- In patients receiving moderately emetogenic chemotherapy and combinations of anthracycline and cyclophosphamide in cycle 1, the most common adverse reactions reported at an incidence of $\geq 5\%$ and a frequency greater than control were decreased appetite (9% VARUBI vs 7% control), neutropenia (7% vs 6%), and dizziness (6% vs 4%)

Just be *Mary* • Just be *Mona* • Just be *myself*

Just be.

Because delayed CINV shouldn't define her.

A single dose of VARUBI® (rolapitant) as part of an antiemetic regimen provides¹:

- The confidence to extend protection against delayed CINV (25-120 h)
- The flexibility to be combined with your preferred 5-HT₃ receptor antagonist and dexamethasone

VARUBI is available as a single dose wallet card containing two 90-mg tablets.

CINV, chemotherapy-induced nausea and vomiting.

Drug interactions

- VARUBI is an inhibitor of breast cancer resistance protein (BCRP) and P-glycoprotein (P-gp). Increased plasma concentrations of BCRP and P-gp substrates with a narrow therapeutic index may result in potential adverse reactions. Monitor for adverse reactions related to the concomitant drug if use with VARUBI cannot be avoided
- Avoid use of VARUBI in patients who require chronic administration of strong CYP3A4 inducers (eg, rifampin) as significantly reduced plasma concentrations of VARUBI can decrease the efficacy of VARUBI

Please see Brief Summary of Prescribing Information for VARUBI on the following page. The full Prescribing Information is available at VarubiRx.com.



VARUBI[®]
rolapitant

 **TESARO**[™]

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Reference: 1. VARUBI [package insert]. Waltham, MA: TESARO, Inc.; 2015.



Brief Summary of Prescribing Information for VARUBI® (rolapitant)

See package insert for full Prescribing Information

INDICATIONS AND USAGE

VARUBI is a substance P/neurokinin 1 (NK1) receptor antagonist indicated in combination with other antiemetic agents in adults for the prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy.

DOSAGE AND ADMINISTRATION

Prevention of Nausea and Vomiting Associated with Emetogenic Cancer Chemotherapy

The recommended dosage of VARUBI in adults in combination with a 5-HT₃ receptor antagonist and dexamethasone is shown in Table 1. There is no drug interaction between rolapitant and dexamethasone, so no dosage adjustment for dexamethasone is required. Administer a dexamethasone dose of 20 mg on Day 1.

Administer VARUBI prior to the initiation of each chemotherapy cycle but at no less than 2- week intervals.

Administer VARUBI without regards to meals.

Table 1: Recommended Dosing Regimen

	Day 1	Day 2	Day 3	Day 4	
Prevention of Nausea and Vomiting Associated with Cisplatin-Based Highly Emetogenic Cancer Chemotherapy					
VARUBI	180 mg; Approximately 1 to 2 hours prior to chemotherapy	None			
Dexamethasone	20 mg; 30 min prior to chemotherapy	8 mg twice daily	8 mg twice daily	8 mg twice daily	
5-HT ₃ receptor antagonist	See the prescribing information for the co-administered 5-HT ₃ receptor antagonist for appropriate dosing information.	None			
Prevention of Nausea and Vomiting Associated with Moderately Emetogenic Cancer Chemotherapy and Combinations of Anthracycline and Cyclophosphamide					
VARUBI	180 mg; Approximately 1 to 2 hours prior to chemotherapy	None			
Dexamethasone	20 mg; 30 min prior to chemotherapy	None			
5-HT ₃ receptor antagonist	See the prescribing information for the co-administered 5-HT ₃ receptor antagonist for appropriate dosing information.	See the prescribing information for the co-administered 5-HT ₃ receptor antagonist for appropriate dosing information.			

DOSAGE FORMS AND STRENGTHS

Tablets: 90 mg rolapitant; film-coated capsule shaped, blue tablets, debossed with T0101 on one side and 100 on the other side.

CONTRAINDICATIONS

VARUBI is contraindicated in patients receiving thioridazine, a CYP2D6 substrate. A significant increase in plasma concentrations of thioridazine may result in QT prolongation and Torsades de Pointes.

WARNINGS AND PRECAUTIONS

Interaction with CYP2D6 Substrates with a Narrow Therapeutic Index

The inhibitory effect of VARUBI on CYP2D6 lasts at least 7 days and may last longer after a single dose administration of VARUBI [see *Contraindications, Drug Interactions*]. Avoid use of VARUBI in patients who are receiving pimozone, a CYP2D6 substrate. An increase in plasma concentrations of pimozone may result in QT prolongation. Monitor for adverse reactions if concomitant use of VARUBI and other CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety of VARUBI was evaluated in approximately 2800 patients in 4 controlled clinical trials in patients receiving emetogenic cancer chemotherapy. VARUBI was given in combination with a 5-HT₃ receptor antagonist and dexamethasone. On Day 1 of Cycle 1 of chemotherapy, 1567 patients were treated with VARUBI and 1198 of these patients continued into the optional multiple cycle extension for up to 6 cycles of chemotherapy. The median number of cycles administered 180 mg of VARUBI was four. VARUBI 180 mg was administered to 1294 patients.

In Cycle 1 adverse reactions were reported in approximately 7% of patients treated with VARUBI compared with approximately 6% of patients treated with control therapy. The most common adverse reactions reported with an incidence of ≥5% and greater than control are listed in Table 2 and Table 3.

Table 2: Most Common Adverse Reactions in Patients Receiving Cisplatin-based Highly Emetogenic Chemotherapy (Cycle 1)*

	VARUBI Regimen (VARUBI, Dexamethasone, and 5-HT ₃ Receptor Antagonist) N = 624	Control (Placebo, Dexamethasone, and 5-HT ₃ Receptor Antagonist) N = 627
Neutropenia	9%	8%
Hiccups	5%	4%

* all reactions occurring at ≥ 5% in the VARUBI group and for which the rate for VARUBI exceeds the rate for control

Table 3: Most Common Adverse Reactions in Patients Receiving Moderately Emetogenic Chemotherapy and Combinations of Anthracycline and Cyclophosphamide (Cycle 1)*

	VARUBI Regimen (VARUBI, Dexamethasone, and 5-HT ₃ Receptor Antagonist) N = 670	Control (Placebo, Dexamethasone, and 5-HT ₃ Receptor Antagonist) N = 674
Decreased appetite	9%	7%
Neutropenia	7%	6%
Dizziness	6%	4%

* all reactions occurring at ≥ 5% in the VARUBI group and for which the rate for VARUBI exceeds the rate for control

Adverse reactions in the multiple-cycle extensions of highly and moderately emetogenic chemotherapy studies for up to 6 cycles of chemotherapy were generally similar to that observed in Cycle 1.

DRUG INTERACTIONS

Effect of VARUBI on Other Drugs

Rolapitant is not an inhibitor or inducer of CYP3A4. Therefore, no dosage adjustment for dexamethasone (CYP3A4 substrate) is needed when co-administered with VARUBI [see *Dosage and Administration*].

Rolapitant is a moderate CYP2D6 inhibitor, an inhibitor of Breast-Cancer-Resistance Protein (BCRP) and an inhibitor of P-glycoprotein (P-gp).

CYP2D6 Substrates with a Narrow Therapeutic Index: Increased plasma concentration of CYP2D6 substrates may result in potential adverse reactions. A three-fold increase in the exposure of dextromethorphan, a CYP2D6 substrate, was observed 7 days after a single dose of VARUBI. The duration of CYP2D6 inhibition was not studied beyond 7 days and may last longer. Concomitant use with thioridazine is contraindicated [see *Contraindications*]. Avoid use of VARUBI with pimozone [see *Warnings and Precautions*]. Monitor for QT prolongation if concomitant use with pimozone cannot be avoided. Monitor for adverse reactions if concomitant use with CYP2D6 substrates with a narrow therapeutic index cannot be avoided.

BCRP Substrates with a Narrow Therapeutic Index (e.g., methotrexate, topotecan, or irinotecan): Increased plasma concentrations of BCRP substrates may result in potential adverse reactions.

Monitor for adverse reactions related to the concomitant drug if use of VARUBI cannot be avoided. Use the lowest effective dose of rosuvastatin (see prescribing information for additional information on recommended dosing).

P-gp Substrates with a Narrow Therapeutic Index: Increased plasma concentrations of digoxin, or other P-gp substrates, may result in potential adverse reactions. Monitor for increased digoxin concentrations. Monitor for adverse reactions if concomitant use of VARUBI with other P-gp substrates with a narrow therapeutic index cannot be avoided.

Effect of Other Drugs on VARUBI

Strong CYP3A4 Inducers (e.g., rifampin): significantly reduced plasma concentrations of rolapitant can decrease the efficacy of VARUBI; avoid use of VARUBI in patients who require chronic administration of such drugs.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no available data on VARUBI use in pregnant women to inform any drug associated risks. In animal reproduction studies, there were no teratogenic or embryo-fetal effects observed with oral administration of rolapitant hydrochloride in rats and rabbits during the period of organogenesis at doses up to 1.2 times and 2.9 times, respectively, the maximum recommended human dose (MRHD) [see Data]. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Data

Animal Data

The potential embryo-fetal toxicity of rolapitant hydrochloride was assessed in pregnant rats administered oral doses equivalent to up to 22.5 mg/kg per day rolapitant free base throughout organogenesis. Rats administered doses equivalent to 13.5 or 22.5 mg/kg per day rolapitant free base exhibited evidence of maternal toxicity including decreased body weight gain and/or body weight loss and a concomitant decrease in food consumption during the first week of dosing. No teratogenic or embryo-fetal effects were observed at doses equivalent to up to 22.5 mg/kg per day rolapitant free base (approximately 1.2 times the recommended human dose on a body surface area basis). In rabbits administered rolapitant hydrochloride throughout the period of organogenesis, oral doses equivalent to up to 27 mg/kg per day rolapitant free base (approximately 2.9 times the recommended human dose on a body surface area basis) were without effects on the developing fetus.

The pre- and postnatal developmental effects of rolapitant hydrochloride were assessed in rats administered oral doses equivalent to 2.25, 9 or 22.5 mg/kg per day rolapitant free base during the periods of organogenesis and lactation. Maternal toxicity was evident based on mortality/moribund condition, decreased body weight and food consumption, total litter loss, prolonged parturition, decreased length of gestation, and increased number of unaccounted for implantation sites at a dose equivalent to 22.5 mg/kg per day free base (approximately 1.2 times the recommended human dose on a body surface area basis). Effects on offspring at this dose included decreased postnatal survival, and decreased body weights and body weight gain, and may be related to the maternal toxicity observed. At a maternal dose equivalent to 9 mg/kg per day rolapitant free base (approximately 0.5 times the recommended human dose on a body surface area basis), there was a decrease in memory in female pups in a maze test and a decrease in pup body weight.

Lactation

Risk Summary

There are no data on the presence of rolapitant in human milk, the effects of rolapitant in the breastfed infant, or the effects of rolapitant on milk production. Rolapitant hydrochloride administered orally to lactating female rats was present in milk [see Data]. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VARUBI and any potential adverse effects on the breastfed infant from VARUBI or from the underlying maternal condition or the use of concomitant chemotherapy.

Data

Radioactivity from labeled [¹⁴C] rolapitant hydrochloride was transferred into milk of lactating rats following a single oral dose equivalent to 22.5 mg/kg rolapitant free base, and the maximum radioactivity in milk was observed at 12 hours post-dose. The mean milk/plasma radioactivity concentration ratios in dams at 1 to 48 hours post-dose ranged from 1.24 to 3.25. Based on average daily consumption of milk (2 mL/day) and the maximum milk radioactivity determined, pup exposure is expected to be 0.32% of the orally administered dose.

Pediatric Use

Safety and efficacy of VARUBI have not been established in pediatric patients.

Geriatric Use

Of the 1294 subjects treated with VARUBI, 25% were 65 years and over, while 5% were 75 and over. No overall differences in safety or efficacy were reported between the elderly subjects and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Hepatic Impairment

No dosage adjustment is needed in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. There are no clinical or pharmacokinetic data in patients with severe hepatic impairment (Child-Pugh Class C). Avoid use of VARUBI in patients with severe hepatic impairment. If use cannot be avoided, monitor patients for adverse reactions related to rolapitant [see *Adverse Reactions*].

Following administration of a single dose of 180 mg rolapitant to patients with mild hepatic impairment (Child-Pugh Class A), the pharmacokinetics of rolapitant were comparable with those of healthy subjects. In patients with moderate hepatic impairment (Child-Pugh Class B), the mean C_{max} was 25% lower while mean AUC of rolapitant was similar compared to those of healthy subjects. The median T_{max} for M19 was delayed to 204 hours in patients with mild or moderate hepatic impairment compared to 168 hours in healthy subjects. The pharmacokinetics of rolapitant was not studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal Impairment

In population pharmacokinetic analyses, creatinine clearance (CL_{Cr}) at baseline did not show a significant effect on rolapitant pharmacokinetics in cancer patients with mild (CL_{Cr}: 60 to 90 mL/min) or moderate (CL_{Cr}: 30 to 60 mL/min) renal impairment compared to cancer patients with normal kidney function. Information is insufficient for the effect of severe renal impairment. The pharmacokinetics of rolapitant was not studied in patients with end-stage renal disease requiring hemodialysis.

OVERDOSAGE

There are no data on overdose with VARUBI.

There is no antidote for VARUBI overdose. Discontinue VARUBI in the event of overdose, and institute general supportive measures and close observation.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Drug Interactions

Advise patients to tell their healthcare provider when they start or stop taking any concomitant medications. VARUBI is a moderate CYP2D6 inhibitor and can increase plasma concentrations of CYP2D6 substrates if they are co-administered. The inhibitory effect of VARUBI on CYP2D6 lasts at least 7 days and may last longer than 7 days after a single dose [See *Contraindications, Warnings and Precautions, Drug Interactions*].

Manufactured for:

TESARO Inc.
1000 Winter St., #3300
Waltham, MA 02451

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Rolapitant for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients With Breast Cancer

Chemotherapy-induced nausea and vomiting (CINV) is commonly associated with anti-neoplastic treatment. It is categorized into 3 main phases. The acute phase occurs within 24 hours of chemotherapy administration, the delayed phase occurs from 24 to 120 hours after chemotherapy administration, and the overall phase encompasses 0 through 120 hours after administration. Acute-phase CINV is mediated primarily by peripherally released serotonin that binds to 5-hydroxytryptamine (5-HT₃) receptors in the vagal afferent neurons. Delayed-phase CINV is caused primarily by binding of substance P to the central neurokinin-1 (NK₁) receptors. CINV causes many patients extreme stress while decreasing quality of life and functional status.^{1,2} Female sex and young age are 2 risk factors for CINV.

Rolapitant is a selective, long-acting NK₁ receptor antagonist. In September 2015, the US Food and Drug Administration (FDA) approved rolapitant, in an oral formulation, for use in combination with a 5-HT₃ receptor antagonist plus dexamethasone for the prevention of delayed CINV in adults receiving moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC).³ The approval was based on three global, double-blind, randomized, placebo-controlled phase 3 trials showing that oral rolapitant (180 mg) improved control of CINV when added to standard treatment among patients receiving HEC or MEC.^{4,5} An intravenous (IV) formulation is currently under review by the FDA.

Breast cancer is the most common malignancy diagnosed in women around the world.⁶ Many of these patients receive chemotherapy regimens that include

anthracyclines and are therefore highly emetogenic. Approximately half of breast cancer patients are diagnosed before age 60 years, imparting a high risk of CINV. Dr Lee Schwartzberg presented results from a post hoc subgroup analysis of the rolapitant MEC trial, focusing on patients with breast cancer. The MEC trial included patients treated with an anthracycline plus cyclophosphamide (AC), which was considered a moderate emetic risk at the time of the trial design.⁷ In this international, double-blind, placebo-controlled, phase 3 trial, the addition of rolapitant (180 mg) demonstrated efficacy and safety in the prevention of delayed CINV in patients receiving MEC regimens.⁵ The trial enrolled 1332 patients at 170 cancer centers in 23 countries. MEC regimens included carboplatin, cyclophosphamide, doxorubicin, and/or fluorouracil. Patients were stratified by sex and then randomly assigned to receive rolapitant (180 mg) or placebo

in combination with dexamethasone (20 mg) on day 1 and granisetron (2 mg) on days 1 to 3. The trial's primary endpoint was the rate of complete response (CR) for delayed emesis. Secondary endpoints included the CR rate during the acute and overall phases. In the overall study population, rolapitant (n=666) showed a 10% improvement over placebo (n=666; 71.3% vs 61.6%; *P*=.002) in the delayed-phase CR rate, thus achieving the primary endpoint (Figure 1). This improvement carried through to the overall phase (68.6% vs 58.1%; *P*<.001), but was not evident during the acute phase (83.5% with rolapitant vs 80.3% with placebo; *P*=.1425).

Breast cancer patients represented approximately two-thirds of the overall study population. Among the entire subpopulation of breast cancer patients, 417 received rolapitant and 428 received placebo. These patients had a median age of 53 to 54 years (range, 22-86 years).

ABSTRACT SUMMARY Single Ascending Dose Pharmacokinetics of Rolapitant Administered Intravenously at Supratherapeutic Doses in Healthy Volunteers

A 2-part, open-label, single-ascending dose study was performed to evaluate the safety and tolerability of IV rolapitant at supratherapeutic doses in healthy volunteers (Abstract 0489). In part 1, 36 healthy subjects received a 30-minute infusion of rolapitant (202.5 mg to 270 mg). In part 2, 64 subjects received a single 30-minute infusion of rolapitant (270 mg) for further safety evaluation. Based on AUC analysis, the plasma concentration of rolapitant increased proportionately across the dose range. *C*_{max} appeared to increase proportionately with the dose, with some variation seen at dose 247.5 mg. In subjects who received the 270 mg dose, the mean *C*_{max} was approximately 3500 ng/mL to 3700 ng/mL, demonstrating a *C*_{max} similar to that observed in prior studies of subjects who received oral rolapitant (720 mg). The mean half-life of IV rolapitant ranged from 135 hours to 155 hours, which was consistent with results from oral rolapitant. The pharmacokinetics of the rolapitant metabolite, M19, were also similar to those observed with the oral formulation of the drug. There were no serious AEs or severe treatment-emergent AEs related to the study drug.

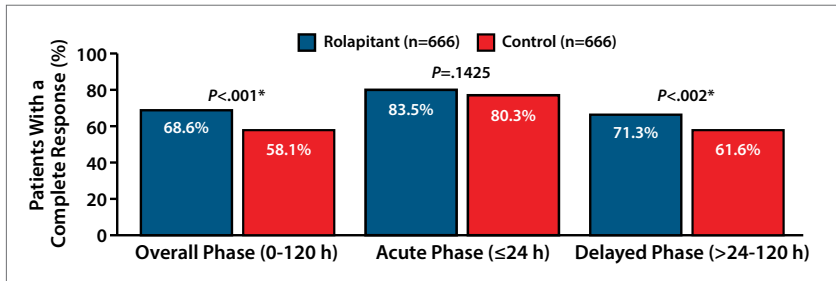


Figure 1. In a phase 3 trial, control of CINV during the overall and delayed phases improved with the addition of rolapitant to granisetron and dexamethasone. CINV, chemotherapy-induced nausea and vomiting. Adapted from Schwartzberg LS et al. *Lancet Oncol.* 2015;16(9):1071-1078⁵ and Schwartzberg LS et al. Abstract MASCC-0316. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.⁷

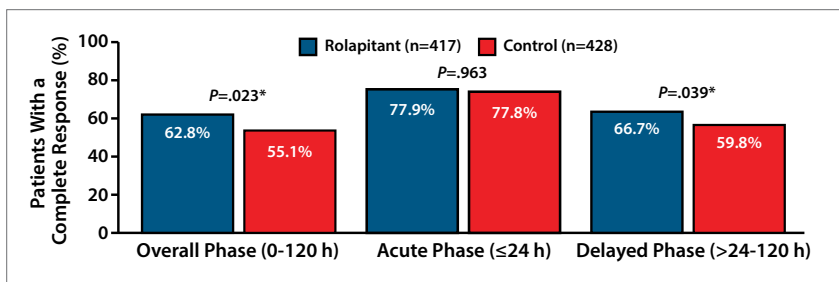


Figure 2. In an analysis of patients with breast cancer, the addition of rolapitant to granisetron and dexamethasone improved control of CINV during the overall and delayed phases. CINV, chemotherapy-induced nausea and vomiting. Adapted from Schwartzberg LS et al. *Lancet Oncol.* 2015;16(9):1071-1078⁵ and Schwartzberg LS et al. Abstract MASCC-0316. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.⁷

Among the subset of breast cancer patients treated with AC chemotherapy, 333 received rolapitant and 347 received placebo. For the entire subgroup of breast cancer patients, rolapitant demonstrated superior control of CINV during the delayed phase (66.7% vs 59.8%; $P = .039$) and the overall phase (62.8% vs 55.1%; $P = .023$), but was similar to placebo during the acute phase (77.9% with rolapitant vs 77.8% with placebo; $P = .963$; Figure 2). The subset of breast cancer patients who received AC chemotherapy yielded similar results, with a significant improvement provided by rolapitant (66.7%) vs placebo (58.8%; $P = .034$). Again, rolapitant showed superior CINV control during the overall phase (62.5% vs 53.9%; $P = .024$), but did not demonstrate an advantage during the acute phase (76.0% with rolapitant vs 76.7% with placebo; $P = .835$).

Rolapitant increased the proportion of patients without emesis during the delayed phase (77.2% vs 68.7%; $P = .005$) and in the overall phase (74.3% vs 62.6%; $P < .001$). No significant improvement was observed during the acute phase (84.4% with rolapitant vs 82.5% with placebo; $P = .351$). Similar improvements were obtained in the breast cancer patients who received AC treatment for the delayed phase ($P = .007$) and the overall phase ($P < .001$), with no significant improvement in the acute phase ($P = .359$). Throughout all phases, the rates of nausea, significant nausea, and complete protection did not differ significantly between the rolapitant and placebo arms. For the entire breast cancer population in the overall phase, no nausea was observed in 35.5% who received rolapitant vs 37.4%

who received placebo ($P = .520$). Thus, control of nausea remains an unmet need in breast cancer patients receiving MEC or AC-based chemotherapy.

Consistent with the results observed in the entire study population, similar safety profiles were observed for breast cancer patients treated with rolapitant or placebo. Approximately 69% of patients had at least 1 treatment-emergent adverse event (AE). The proportion of patients with a treatment-related AE was 11.2% in the rolapitant group vs 8.8% in the control group. Among patients treated with AC, treatment-related AEs occurred in 9.0% vs 8.8%, respectively. Treatment-emergent AEs causing discontinuation of the study drug occurred in 0.7% of the rolapitant group vs 1.2% of the placebo group. The most common treatment-related AEs were constipation, headache, and fatigue, occurring in 2.3% to 3.3% of patients. No unexpected AEs emerged.

References

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Rolapitant for Control of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients With Lung Cancer

Three pivotal phase 3 trials demonstrated that the addition of a single dose of oral rolapitant to standard therapy reduced the incidence of delayed CINV in patients receiving MEC or HEC.^{1,2} The Highly Emetogenic Chemotherapy trials 1 and 2 (HEC-1 and HEC-2) evaluated cisplatin-based chemotherapy.¹ Patients were randomly assigned to receive rolapitant (180 mg on day 1) or matching placebo, plus granisetron (10 µg/kg on day 1), and dexamethasone (20 mg on day 1 followed by 8 mg twice daily, on days 2-4). In the overall study population of 1070 patients who were receiving cisplatin-based treatment, the addition of rolapitant resulted in a significant improvement in delayed-phase CINV control over placebo (71% vs 60%; $P=.0001$), thus meeting the primary endpoint. The study met its secondary endpoints as well, demonstrating improved CINV control during the acute phase (82% vs 77%; $P=.0045$) and the overall phase (69% vs 59%; $P=.0005$). A companion trial by Schwartzberg and colleagues investigated the addition of rolapitant to dexamethasone plus granisetron in patients with various cancer types who were receiving MEC or AC.² In this study, oral rolapitant demonstrated a 10% improvement over placebo for the delayed-phase CR rate (71.3% vs 61.6%; $P=.002$), thus achieving the primary endpoint.

Dr Rudolph Navari presented results from a post hoc analysis of the subgroup of lung cancer patients included in these 3 trials, with 337 patients in the rolapitant subgroup and 350 in the control group.³ The rolapitant vs placebo groups were well-balanced with respect to age, sex, alcohol consumption, region, and chemotherapies. Patients had a median age of 61 to 62 years (range, 24-88

Table 1. Prevention of CINV Among Patients With Lung Cancer Receiving Standard Treatment With or Without Rolapitant

Endpoint (%)	Rolapitant (n=337)	Control (n=350)	Δ	P Value
Complete Response				
Overall phase (0-120 h)	75.4	63.1	12.3	<.001
Acute phase (≤24 h)	88.4	81.7	6.7	.014
Delayed phase (>24-120 h)	77.4	65.1	12.3	<.001
No Emesis				
Overall phase (0-120 h)	79.8	67.7	12.1	<.001
Acute phase (≤24 h)	91.1	84.6	6.5	.009
Delayed phase (>24-120 h)	81.0	69.7	11.3	<.001
No Nausea				
Overall phase (0-120 h)	60.5	48.6	11.9	<.002
Acute phase (≤24 h)	75.7	70.9	4.8	.155
Delayed phase (>24-120 h)	63.5	51.1	12.4	.001
Complete Protection				
Overall phase (0-120 h)	70.9	58.6	12.3	<.001
Acute phase (≤24 h)	86.1	80.3	5.8	.044
Delayed phase (>24-120 h)	73.0	60.3	12.7	<.001

CINV, chemotherapy-induced nausea and vomiting.

Adapted from Navari RM et al. Abstract MASCC-0321. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.³

ABSTRACT SUMMARY Trial of Antiemetic Triplet Therapy Comparing Palonosetron and Granisetron in Breast Cancer Patients Receiving AC Chemotherapy: Double Blind Randomised Comparative Phase III Study

The antiemetic efficacy of palonosetron was compared with that of granisetron as part of triplet therapy for breast cancer patients receiving AC chemotherapy in a double-blind, randomized phase 3 trial (Abstract 0245). The study included 491 women with breast cancer from 11 institutions. Most patients were outpatients with access to metoclopramide as rescue medicine. Patients were stratified according to age, institution, and habitual alcohol intake. They were randomly assigned to receive a single dose of either palonosetron (0.75 mg) or granisetron (40 mg/kg) 30 minutes before AC chemotherapy on day 1. In addition, patients received IV dexamethasone (9.9 mg) and oral aprepitant (125 mg) on day 1, plus oral aprepitant (80 mg) on days 2 and 3. Patients who received palonosetron achieved a numerically superior CR rate compared with those who received granisetron (58.5% vs 53.8%), but the difference was not significant. The incidence of vomiting is being examined as a secondary endpoint of the same study.

years). In both arms, approximately 70% of patients were male. In the rolapitant group, the chemotherapy regimens included cisplatin in 70.0% and carboplatin in 29.4% (vs 65.7% and 32.6% in the placebo group).

For lung cancer patients treated with either cisplatin or carboplatin, the addition of oral rolapitant provided significantly more protection against CINV than placebo. The trial met its primary endpoint, demonstrating increased control of CINV when rolapitant was added to a 5-HT₃ receptor antagonist plus dexamethasone (77.4% vs 65.1%; $P < .001$; Table 1). Rolapitant also demonstrated an increased CR rate vs placebo in the acute phase (88.4% vs 82.7%; $P = .014$) and the overall phase (75.4% vs 63.1%; $P < .001$). Emesis control was superior with rolapitant vs placebo in the delayed phase (81.0% vs 69.7%; $P < .001$), the acute phase (91.1% vs 84.6%; $P = .009$), and the overall phase (79.8% vs 67.7%; $P < .001$). In contrast to the breast cancer

subgroup,⁴ in the lung cancer population, the addition of rolapitant reduced the proportion of patients experiencing nausea in the delayed and overall phases. The proportions of patients with no nausea were 63.5% with rolapitant vs 51.1% with placebo in the delayed phase ($P = .001$), 75.7% vs 70.9% in the acute phase ($P = .155$), and 60.5% vs 48.6% in the overall phase ($P = .002$). The demonstration of nausea control stands in contrast to results observed with other NK₁ receptor antagonists. Significantly improved rates of complete protection were also observed in lung cancer patients who received rolapitant vs placebo, at 73.0% vs 60.3% for the delayed phase ($P < .001$), 86.1% vs 80.3% for the acute phase ($P = .044$), and 70.9% vs 58.6% for the overall phase ($P < .001$).

No new safety signals emerged in patients who received rolapitant. The rolapitant and control groups demonstrated similar safety profiles. Treatment-emergent AEs were

reported in 58.0% of the rolapitant group vs 58.1% of the placebo group.

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Quality of Life, Efficacy and Patient-Reported Outcome With NEPA as CINV Prophylaxis in Highly or Moderately Emetogenic Chemotherapy

The fixed-dose oral combination tablet NEPA was approved by the FDA in October 2014 for the management of acute and delayed CINV during initial and subsequent cycles of HEC or MEC.¹ NEPA contains netupitant (300 mg) and palonosetron (0.5 mg). Netupitant is an NK₁ receptor antagonist, and palonosetron is a 5-HT₃ receptor antagonist. Netupitant has an 8-fold longer half-life than its predecessor, aprepitant, and has high binding affinity to NK₁ receptors. Palonosetron is a second-generation serotonin receptor antagonist with antiemetic activity at central and gastrointestinal sites.^{2,3} Compared with first-generation 5-HT₃ receptor antagonists, palonosetron has a

30-fold higher receptor binding affinity and a longer half-life that confer higher potency. Palonosetron has also demonstrated superior tolerability compared with other serotonin receptor antagonists.

Dr Petra Feyer presented preliminary results of a study evaluating quality of life, efficacy, and patient-reported outcomes with NEPA in patients receiving MEC or HEC on 1 or 2 days per cycle.⁴ The multicenter, prospective, noninterventional study has a planned enrollment of 2500 patients at 200 centers in Germany and an observation period of 2 years. The study's primary endpoint is quality of life based on the Functional Living Index—Emesis (FLIE) questionnaire.

The secondary endpoints include efficacy, safety, and use of rescue medication. Patients receive documented antiemetic prophylaxis with NEPA during 3 consecutive chemotherapy cycles. After the completion of each chemotherapy cycle, NEPA efficacy is evaluated and electronically documented by physicians using a 4-point scale representing very good, good, satisfactory, or poor. Patients are required to keep a diary reporting use of rescue medication as well as levels of emesis and vomiting using a 4-point scale indicating no, rare, moderate, or strong symptoms, with separate reporting for anticipatory nausea and vomiting.

The study population consisted of adults who were receiving treatment

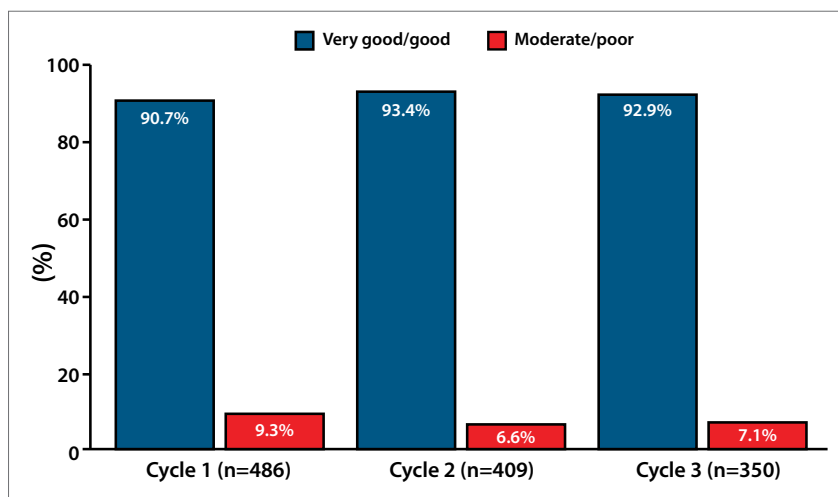


Figure 3. Physician assessment of the efficacy of NEPA in preventing vomiting and avoiding the need for rescue therapy among patients receiving highly or moderately emetogenic chemotherapy in an interim analysis of a multicenter, prospective, open, noninterventional study. NEPA, netupitant and palonosetron. Adapted from Feyer P et al. Abstract MASCC-0289. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.⁴

ABSTRACT SUMMARY Rolapitant for the Prevention of Nausea in Patients Receiving Moderately or Highly Emetogenic Chemotherapy

Data from the pivotal phase 3 trials of rolapitant were analyzed for control of chemotherapy-induced nausea (Abstract 0322). Nausea was self-assessed by patients for 5 days following chemotherapy using a visual analog scale to indicate severity. Patients self-assessed the impact of CINV on daily life using the validated FLIE questionnaire on day 5 after chemotherapy. All patients included in the analysis received at least 1 dose of study drug. During the overall and delayed phases, 42% to 54% of patients receiving control therapy reported no nausea. Rolapitant consistently provided an 11% improvement in rates of no nausea relative to the control arm. Rolapitant significantly improved rates of no nausea or no significant nausea in patients treated with cisplatin-based chemotherapy ($P=.020$) and in the combined cohort of patients treated with carboplatin-based chemotherapy or other types ($P=.010$). Among patients receiving AC-based chemotherapy, however, nausea domain scores were similar, at 51.2% with rolapitant and 50.2% with placebo ($P=.440$).

with MEC or HEC in regimens of 1 or 2 days. NEPA was administered based on the physician's choice. Between September 2015 and June 2016, the study recruited 704 patients. Among the

583 patients available for preliminary analysis, the median age was 56 years (range, 28-88 years), and 89% were female. The majority of patients had breast cancer (71.0%), followed by

cancer of the ovary (7.7%), colon or rectum (4.8%), lung (4.5%), stomach (2.1%), pancreas (1.9%), head and neck (1.2%), and cervix (1.0%). The Eastern Cooperative Oncology Group (ECOG) performance status was 0 in 57.6%, 1 in 35.0%, and 2 in 7.4%. Chemotherapy was administered in the adjuvant setting in 50.9%, the neoadjuvant setting in 26.7%, and as palliative care in 22.4%. Treatment regimens included AC-based chemotherapy in 55.9%, carboplatin in 17.7%, cisplatin in 7.5%, oxaliplatin in 6.5%, other MECs in 6.3%, and low emetogenic chemotherapy in 6.1%.

The analysis included 486, 409, and 350 patients with data from chemotherapy cycles 1, 2, and 3, respectively. Based on physician evaluation, NEPA efficacy was very good or good in 90.7% of patients in cycle 1, 93.4% in cycle 2, and 92.9% in cycle 3 (Figure 3). During cycle 1, self-assessments from 87 patients demonstrated a high CR rate. There was no emesis or use of rescue medication during the acute phase in 88.8% of patients, during the delayed phase in 85.1%, and during the overall phase in 79.2%. No emesis was reported by 94% of patients in the acute phase, 99% in the delayed phase, and 93% in the overall phase.

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Olanzapine for the Prophylaxis and Rescue of Chemotherapy-Induced Nausea and Vomiting (CINV): A Retrospective Study

Olanzapine is an established anti-psychotic agent of the thienobenzodiazepine class that targets many different receptors, including the dopaminergic, serotonergic, adrenergic, histaminergic, and muscarinic receptors.¹⁻⁵ It has demonstrated efficacy in the setting of CINV prophylaxis among patients receiving treatment with MEC or HEC, but little information is available regarding its use as rescue medication for breakthrough CINV.

Olanzapine was compared with metoclopramide for the ability to control breakthrough CINV in a double-blind, randomized phase 3 trial.⁶ The study included chemotherapy-naive patients receiving HEC containing cisplatin or doxorubicin plus cyclophosphamide. All patients received prophylactic palonosetron, fosaprepitant, and dexamethasone. Patients were randomized to receive oral olanzapine (10 mg daily for 3 days) or oral metoclopramide (10 mg 3 times daily for 3 days). Of the 276 randomized patients, 112 developed breakthrough CINV, and 108 were evaluable. During the 72-hour observation period after administration of therapy for breakthrough CINV, no emesis occurred in 70% of patients treated with olanzapine vs 31% of patients treated with metoclopramide ($P<.01$). Olanzapine was also associated with a higher proportion of patients who did not report nausea (68% vs 23%; $P<.01$).

Dr Leonard Chiu presented results of a study that retrospectively evaluated the safety and efficacy of olanzapine for the treatment of breakthrough CINV, with additional data on the efficacy and safety of the drug's use in the prophylactic setting in a smaller cohort of patients.⁷ A retrospective review was conducted of electronic medical records of adult patients who received a

Table 2. Alleviation of Breakthrough CINV and Prevention of CINV With Olanzapine

	Rescue Setting (n=193) ^a	Prophylaxis Setting (n=20) ^b
Improved nausea	88.1%	100.0%
Improved vomiting	21.8%	35.0%

^aThe total number of chemotherapy cycles, 193, was used to calculate the proportion.

^bThe total number of chemotherapy cycles, 20, was used to calculate the proportion.

CINV, chemotherapy-induced nausea and vomiting.

Adapted from Chiu L et al. Abstract MASCC-0153. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.⁷

Chemotherapy Induced Nausea and Vomiting in Gynecological Cancer Patients: "Treatment-Related" and "Patient-Related" Risk Factors

A study was undertaken to define risk factors that influence the experience of nausea and vomiting after the first therapeutic infusion in 94 patients with gynecologic cancer (Abstract 0419). Data were gathered from several sources: a questionnaire that collected sociodemographic and clinical information, as well as potential risk factors; the State-Trait Anxiety Inventory, a widely used measure of anxiety in clinical trials; the Multinational Association of Supportive Care in Cancer (MASCC) Antiemesis Tool to assess whether patients receiving chemotherapy are experiencing CINV; and a questionnaire for reporting symptoms. Multiple regression analyses found that patients who were working full-time or part-time were less likely to experience acute or delayed nausea ($P=.002$ and $P=.045$, respectively) than patients who did not work during treatment. Patients who experienced nausea during previous chemotherapy treatments were more likely to experience nausea during the current treatment in the acute ($P=.020$) and delayed ($P=.019$) phases. Acute nausea was more likely in younger patients ($P=.001$) and in patients who habitually ingested alcohol ($P=.047$). Delayed nausea was more likely in patients with a heightened state of anxiety ($P=.029$). Treatment emetogenicity was associated with delayed vomiting ($P=.029$).

prescription for olanzapine from a single hospital-associated pharmacy between January 2013 and June 2015. Included patients had received 1 or more doses of olanzapine for the rescue or prophylaxis of CINV with documentation of the outcome. The analysis included 154 patients and 193 treatment cycles in the rescue setting, as well as 16 patients representing 20 treatment cycles in the prophylactic setting.

In the rescue setting, nausea improved in 88.1% of patients, and

vomiting improved in 21.8% (Table 2). In the prophylactic setting, olanzapine reduced nausea in 100% of patients and vomiting in 35%.

The adverse events included sedation and constipation. Sedation was reported by 42.5% of patients in the breakthrough setting and by 65.0% of patients who received olanzapine as prophylaxis. Constipation occurred in 31.6% of patients in the rescue setting and 35.0% of patients in the prophylactic setting.

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Rolapitant for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients Aged <65 Versus ≥65 Years

Patients younger than 65 years are at increased risk for CINV.^{1,2} Patients ages 65 years and older are at greater risk for CINV-related complications, including dehydration, impaired renal function, and abnormal blood pressure. The efficacy of rolapitant (180 mg) administered as a single dose in combination with a 5-HT₃ receptor antagonist plus dexamethasone has been demonstrated in placebo-controlled, randomized phase 3 trials in patients receiving HEC or MEC.^{3,4} In these pivotal, phase 3 trials, patients recorded emetic episodes and use of rescue medication in diaries for approximately 120 hours following administration of chemotherapy. Each trial had a primary endpoint of CR, defined as no emesis and no use of rescue medication during the delayed phase.

Dr Matti Aapro presented results of an exploratory analysis of pooled data from these phase 3 trials based on patient age (<65 years vs ≥65 years).⁵ The 3 trials included 2402 patients in the modified intent-to-treat population, of whom 73.1% were younger than 65 years and 26.9% were ages 65 years and older. Data from the trials of HEC showed that CR rates were similar for the younger and older patients in the acute phase (76.8% vs 76.1%), delayed

phase (59.8% vs 61.3%), and overall phase (58.5% for both). Data from the placebo arm of the MEC or AC chemotherapy trial showed a trend toward a lower CR rate in younger patients vs older patients in all phases (acute, 56.6% vs 60.7%; delayed, 60.9% vs 63.3; and overall, 56.6% vs 60.7%), consistent with the known increased risk of CINV in younger patients as well as the greater proportion of female patients in the younger cohort.

As was observed in the overall populations of the 3 pivotal studies, the addition of rolapitant improved the CR rate compared with placebo for the cohorts of younger and older patients in the acute, delayed, and overall phases of the HEC-1 and HEC-2 trials and in the delayed and overall phases of the MEC or AC chemotherapy trial. The analysis showed that patients younger than 65 years as well as those ages 65 years or older benefited from the addition

ABSTRACT SUMMARY Effects of Rolapitant Administered Intravenously on the Pharmacokinetics of Digoxin (P-gp) and Sulfasalazine (BCRP) in Healthy Volunteers

An integrated safety analysis from the rolapitant pivotal phase 3 trials showed no evidence of drug interactions when rolapitant was coadministered with P-glycoprotein or therapies that target breast cancer resistance protein substrates (Abstract 0494). An open-label drug-drug interaction study was conducted to evaluate the effects of IV rolapitant on the pharmacokinetics of a P-glycoprotein substrate and a breast cancer resistance protein substrate and to evaluate the safety and tolerability of these drug combinations in healthy volunteers. Patients initially received a single dose of oral digoxin (0.5 mg; n=36) or oral sulfasalazine (500 mg; n=36). After approximately 24 hours, patients then received a second dose of the same substrate plus a single dose of IV rolapitant (166.5 mg). Sulfasalazine (500 mg) was administered a third time on day 13. The introduction of rolapitant did not affect the digoxin AUC and increased the digoxin C_{max} by 21% (GMR, 1.21; 90% CI, 1.07-1.37). Rolapitant decreased the sulfasalazine C_{max} by 18% on day 13 (GMR, 0.82; 90% CI, 0.69-0.97). The drug combinations were well-tolerated, and no clinically significant safety signals emerged.

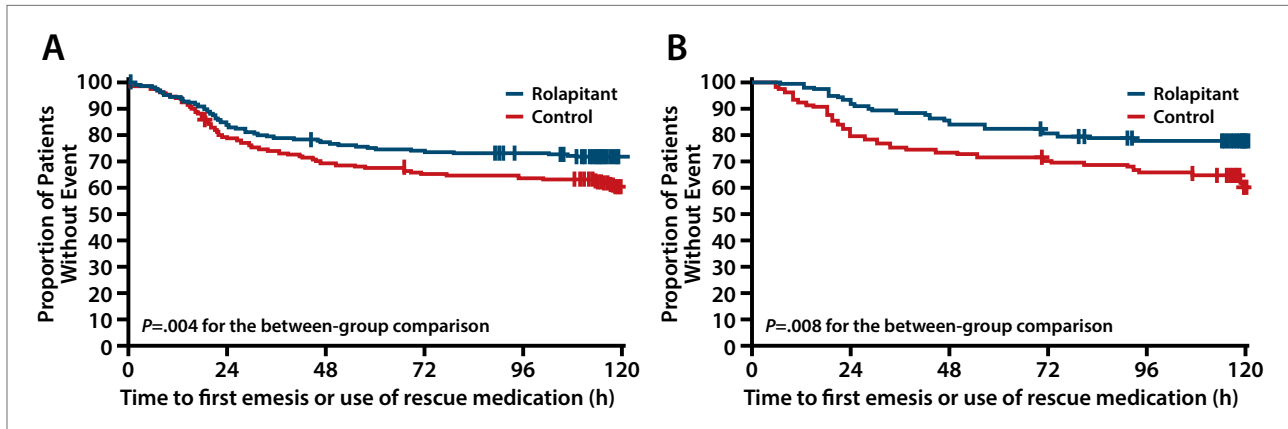


Figure 4. The addition of rolapitant to standard CINV therapy reduced time to first emesis or use of rescue medication in younger patients (A) and older patients (B). These figures illustrate data for patients receiving highly emetogenic chemotherapy. CINV, chemotherapy-induced nausea and vomiting. Adapted from Aapro M et al. Abstract MASCC-0432. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.⁵

of rolapitant to a 5-HT₃ receptor antagonist plus dexamethasone.

Based on Kaplan-Meier analysis of time to first emesis or use of rescue medication, rolapitant protected against CINV during the entire 120-hour study duration in younger patients and older patients in the pooled cohorts from the HEC-1 and HEC-2 trials ($P=.004$ and $P=.008$, respectively; Figure 4) and in patients from the MEC or AC chemotherapy trial ($P=.001$ and $P=.016$, respectively). In the MEC or AC chemotherapy trial, the older patients showed a delayed time to first emesis and delayed use of rescue medication compared with the younger cohort. However, this study had a greater proportion of female patients, who are more likely to develop CINV. Rolapitant was generally well-tolerated in both of the age-based patient cohorts from the 3 pivotal trials.

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ABSTRACT SUMMARY Development of a Prediction Tool for Identifying Patients at High Risk for Chemotherapy-Induced Nausea and Vomiting (CINV)

Pooled data from 4 noninterventional prospective studies were analyzed to identify factors associated with increased risk of CINV in patients receiving outpatient anticancer therapy (Abstract 0602). The study included 1198 patients who received a total of 4197 cycles of chemotherapy. Patients had a median age of 58 years, and 75% were female. Chemotherapeutic regimens included anthracycline in 52.8%, platinum in 27.4%, other types in 12.4%, and taxane monotherapy in 7.4%. More than 60% of patients experienced nausea and/or vomiting during the 5 days after chemotherapy, with 42.2% of patients reporting CINV of at least grade 2. Numerous factors were associated with increased risk of CINV, including platinum- or anthracycline-based chemotherapy (odds ratio [OR], 2.37), use of nonprescribed antiemetics at home (OR, 2.26), CINV during a prior treatment cycle (OR, 1.73), and age younger than 60 years (OR, 1.47). Disease sites with an increased risk of CINV vs breast cancer included genitourinary (OR, 2.43), gastrointestinal (OR, 1.80), gynecologic (OR, 1.43), and other nonlung and nonbreast disease (OR, 1.92). Other factors included early-stage disease (OR, 1.30), patient expecting to develop CINV (OR, 1.38), less than 7 hours of sleep (OR, 1.25), and a history of morning sickness (OR, 1.41). The likelihood of CINV was greatest during the first chemotherapy cycle. The authors presented a CINV prediction tool to aid physicians in evaluating patients at risk of developing CINV. Receiver operator characteristic analysis indicated that the tool provided good predictive accuracy, with an AUC of 0.71 (95% CI, 0.69-0.73) and a close association between score and risk of CINV (OR, 1.18; $P<.001$).

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A Single-Dose Bioequivalence Study of Rolapitant Following Oral and Intravenous Administration in Healthy Volunteers

The FDA approved rolapitant in an oral formulation for the prevention of CINV in the delayed phase based on results of three phase 3 trials.^{1,2} The FDA is currently reviewing an IV formulation of rolapitant. Dr Xiaodong Wang presented results from an open-label, single-center, parallel-group, randomized study that assessed the bioequivalence, safety, and efficacy of a single oral dose of rolapitant (180 mg) administered in four 45-mg capsules vs a single IV dose of rolapitant (166.5 mg) administered via a 30-minute infusion.³ Blood samples were obtained for pharmacokinetic analysis before rolapitant administration and at specified time points up to 912 hours after drug administration. Mean plasma concentration time profiles for rolapitant were generated and evaluated for the maximum concentration (C_{max}) and area under the curve (AUC). Ninety percent confidence intervals (CIs) between 0.80 and 1.25 were specified as equivalence bounds.

Oral rolapitant was administered to 67 patients, and the IV formulation was administered to 71. The study demonstrated bioequivalence of the 2 formulations. The mean plasma concentrations as measured from 0 to 912 hours were similar (Figure 5). The 90% CIs of the geometric least-squares mean ratio (GMR) fell within the pre-specified bounds of 0.80 to 1.25 for all pharmacokinetic parameters, for AUC through the last measured concentration (GMR, 1.01; 90% CI, 0.94-1.09), and for AUC extrapolated to infinity (GMR, 1.01; 90% CI, 0.93-1.10). As anticipated, the C_{max} values were higher following IV administration of rolapitant (GMR=1.90). M19 is a major

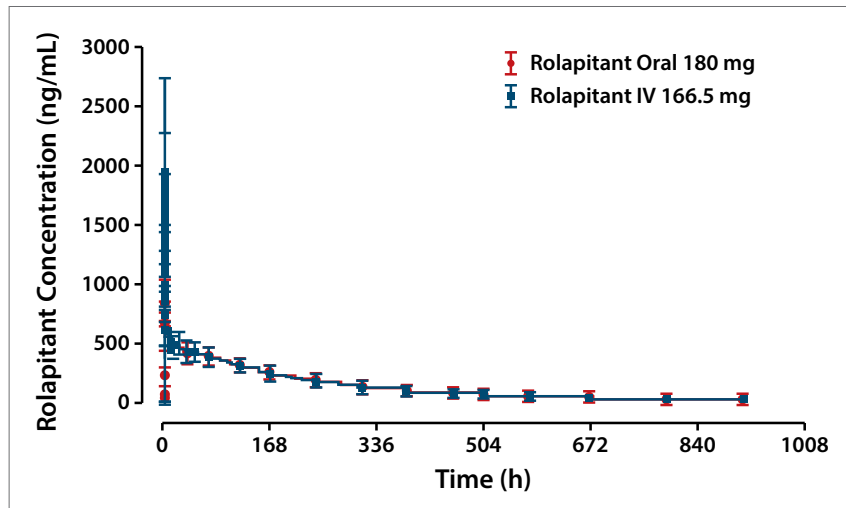


Figure 5. The mean (standard deviation) plasma concentrations for rolapitant administered orally or intravenously (IV) in a time profile from 0 to 912 hours. A linear scale is used. Adapted from Wang X et al. Abstract MASCC-0485. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.³

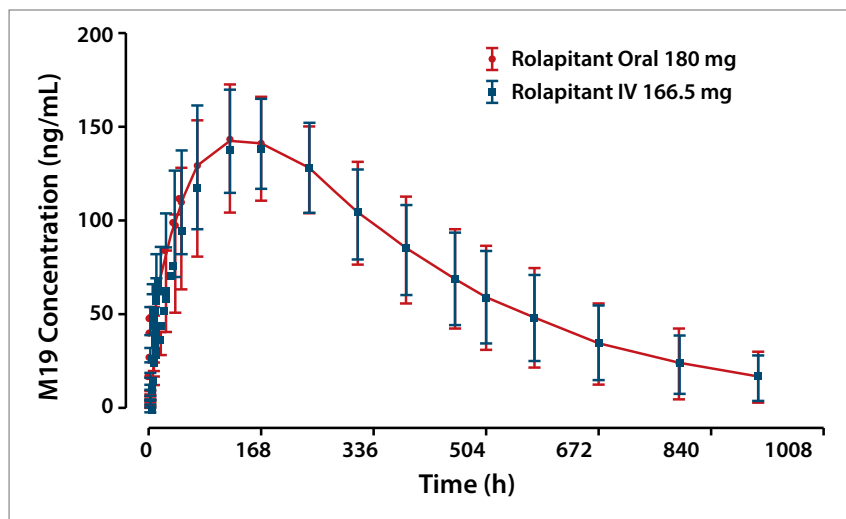


Figure 6. The mean (standard deviation) plasma concentrations of M19, the major metabolite for rolapitant, as measured in doses administered orally or intravenously (IV) in a time profile from 0 to 912 hours. A linear scale is used. Adapted from Wang X et al. Abstract MASCC-0485. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.³

metabolite of rolapitant, and analysis of M19 pharmacokinetic parameters also demonstrated bioequivalence (Figure 6), with GMR values of 0.98 (90% CI, 0.93-1.04) for C_{max} , 0.97 (90% CI, 0.91-1.03) for AUC through the last measured concentration, and 0.95 (90% CI, 0.88-1.03) for AUC extrapolated to infinity.

There were no severe or serious treatment-emergent AEs. No new rolapitant-associated AEs were identified.

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No Signals of Increased Toxicity After Concomitant Administration of NEPA With Etoposide or Docetaxel: Pooled Safety Data From 4 Pivotal Studies

NEPA is an oral, fixed-dose combination of the NK₁ receptor antagonist netupitant and the 5-HT₃ receptor palonosetron. Netupitant also moderately inhibits the cytochrome P450 isoenzyme 3A. Etoposide and docetaxel are metabolized primarily by CYP3A4 and CYP3A5, leading to concerns of potential drug-drug interactions between netupitant and these therapies. Dr Matti Aapro presented

results of a post hoc safety analysis that evaluated toxicities in patients treated with etoposide and/or docetaxel plus either NEPA or palonosetron (oral or IV).¹ The analysis included data from 3280 patients enrolled in a single phase 2 trial or three phase 3 studies.²⁻⁵

The median ages ranged from 53 to 59 years. Most patients who received etoposide were male and had cancer of the lung or respiratory tract. Patients

treated with docetaxel had cancer of the breast, head and neck, lung or respiratory tract, and others. Most patients had an ECOG performance status of 0 or 1.

There were no clinically relevant differences in the frequency of serious AEs or treatment-emergent AEs. In the etoposide cohort, the proportion of patients who experienced at least 1 serious AE was 9.0% with NEPA,

Table 3. Adverse Events in a Pooled Analysis Comparing NEPA vs Palonosetron

	Etoposide Subpopulation			Docetaxel Subpopulation		
	NEPA 300/0.50 mg (n=89)	Oral PALO 0.50 mg (n=85)	IV PALO 0.25 mg (n=45)	NEPA 300/0.50 mg (n=49)	Oral PALO 0.50 mg (n=37)	IV PALO 0.25 mg (n=13)
Total exposures	300	88	45	196	77	13
Number (%) of patients with ≥1 SAE	8 (9.0)	8 (9.4)	6 (13.3)	10 (20.4)	5 (13.5)	4 (30.8)
Number (%) of patients with a TEAE	7 (7.9)	4 (4.7)	6 (13.3)	10 (20.4)	3 (8.1)	2 (15.4)
Anemia	5 (5.6)	1 (1.2)	2 (4.4)	5 (10.2)	–	–
Leukopenia	4 (4.5)	1 (1.2)	2 (4.4)	7 (14.3)	1 (2.7)	–
Neutropenia	3 (3.4)	1 (1.2)	4 (8.9)	6 (12.2)	2 (5.4)	1 (7.7)
Thrombocytopenia	–	–	1 (2.2)	4 (8.2)	1 (2.7)	1 (7.7)
Diarrhea (SAE only)	–	–	–	1 (2.0)	–	–
Infections	2 (2.2)	3 (3.5)	–	9 (18.4)	1 (2.7)	1 (7.7)

IV, intravenous; NEPA, netupitant and palonosetron; PALO, palonosetron; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Adapted from Aapro M et al. Abstract MASCC-0565. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.¹

ABSTRACT SUMMARY Rolapitant for Control of Chemotherapy-Induced Nausea and Vomiting (CINV) in Patients With Gynecologic Cancer

A post hoc analysis of data from the phase 3 trials of IV rolapitant was conducted to evaluate control of CINV in patients with gynecologic cancer (Abstract 0318). The analysis included 106 women who received IV rolapitant (180 mg) and 95 who received placebo. Patients had a median age of 57 years (range, 21-81 years). Tumor sites included the ovary in 59%, the uterus in 29%, and the cervix in 12%. Chemotherapy regimens included cisplatin in 55.2% and carboplatin in 43.8%. CR rates were 9% to 16% higher with rolapitant in the acute ($P=.048$), delayed ($P=.011$), and overall ($P=.012$) phases of CINV. During the overall phase, rolapitant yielded higher rates of no emesis ($P=.016$), no nausea ($P=.004$), and complete protection ($P=.005$), conferring an advantage of approximately 13% to 20% improvement over placebo. Significant improvements with rolapitant were also observed during the delayed phase for rates of no emesis ($P=.023$), no nausea ($P=.007$), and complete protection ($P=.005$). Differences in outcomes during the acute phase were not significant. Some patients continued to experience CINV, particularly nausea, despite treatment with the study drug combination. The overall safety profiles were similar for patients in the rolapitant and placebo arms, with no treatment-related serious AEs and no treatment-related deaths.

9.4% with oral palonosetron, and 13.3% with IV palonosetron (Table 3). The proportions of patients with any treatment-emergent AE were 7.9% with NEPA, 4.7% with oral palonosetron, and 13.3% with

IV palonosetron. In the docetaxel cohort, the proportion of patients who experienced at least 1 serious AE was 20.4% with NEPA, 13.5% with oral palonosetron, and 30.8% with IV palonosetron. The proportions of

patients with any treatment-emergent AE were 20.4%, 8.1%, and 15.4% in the 3 subcohorts, respectively.

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Phase II Study of Palonosetron, Aprepitant, Dexamethasone and Olanzapine for the Prevention of Cisplatin-Based Chemotherapy-Induced Nausea and Vomiting in Patients With Thoracic Malignancy

The 3-drug combination of a 5-HT₃ receptor antagonist, aprepitant, and dexamethasone is recommended for patients receiving HEC. Phase 3 studies investigating this 3-drug combination have reported CINV CR rates of approximately 60% to 70% in the overall phase. Olanzapine inhibits several neurotransmitter pathways that are involved in nausea and vomiting, including those mediated by the serotonergic, dopaminergic, α -1 adrenergic, histaminic, and muscarinic receptors.¹⁻⁴ The combination of olan-

zapine plus standard antiemetic therapy demonstrated efficacy in preventing CINV in several clinical trials of patients receiving HEC.⁵⁻⁷

Dr Kouichi Yokoyama presented results of an open-label, single-center, single-arm phase 2 study that evaluated the combination of olanzapine, palonosetron, aprepitant, and dexamethasone for the prevention of CINV in patients with thoracic malignancy receiving cisplatin-based chemotherapy.⁸ Patients were ages 20 years or older and had histologically

or cytologically confirmed thoracic malignant disease and an ECOG performance status of 0 or 1. All patients received combination chemotherapy that included a minimum cisplatin dose of 60 mg/m². Patients also received oral olanzapine (5 mg) once daily at night on days 1 to 5 in combination with standard antiemetic therapy consisting of IV palonosetron (0.75 mg, day 1), oral aprepitant (125 mg, day 1; 80 mg days, 2 and 3), and IV dexamethasone (9.9 mg, day 1) followed by oral dexamethasone (8 mg, days 2-4). The

ABSTRACT SUMMARY Quantitative Market Research to Identify Factors That Influence Chemotherapy-Induced Nausea and Vomiting (CINV) Treatment Compliance

Adherence to CINV management guidelines is often suboptimal (Aapro M et al. *Ann Oncol*. 2012;23[8]:1986-1992). Oncologists were queried via an online questionnaire regarding perceived patient antiemetic use to determine the rate of antiemetic treatment failure and factors that contribute to patient nonadherence (Abstract 0444). The questionnaire was sent to 300 oncologists in 5 European countries, all of whom prescribed antiemetics and typically saw at least 50 cancer patients per month. Despite antiemetic prophylaxis, emesis rates were higher for patients receiving HEC compared with MEC in the acute phase (21% vs 15%) and the delayed phase (26% vs 18%). In the acute and delayed phases, the most common reason for antiemetic treatment failure was underestimating the emetogenic potential of chemotherapy (43% vs 39%), followed by choosing weaker antiemetic regimens than required (31% vs 33%) and mistakes with administration of antiemetic treatments (21% vs 17%). Oncologists estimated that 35% of patients had adherence issues with administration of antiemetic agents at home. Patient nonadherence with antiemetic treatments was a significant concern for 42% of oncologists.

Table 4. Efficacy of Palonosetron, Aprepitant, Dexamethasone, and Olanzapine in the Prevention of Cisplatin-Based CINV in Patients With Thoracic Malignancy

	Study Phase	Rate (%)	90% CI (%)	95% CI (%)
Complete Response	Acute	100	92-100	89-100
	Delayed	83	70-92	66-93
	Overall	83	70-92	66-93
Complete Control	Acute	93	82-98	79-98
	Delayed	73	59-84	56-86
	Overall	70	55-82	52-83
Total Control Rates	Acute	77	62-87	59-88
	Delayed	70	55-82	52-83
	Overall	63	48-76	46-78

CINV, chemotherapy-induced nausea and vomiting.

Adapted from Yokoyama M et al. Abstract MASCC-0198. Presented at: MASCC/ISOO Annual Meeting on Supportive Care in Cancer; June 23-25, 2016; Adelaide, Australia.⁸

trial's primary endpoint was the CR rate in the overall phase. Secondary endpoints included CR rates in the acute and delayed phases; complete control rates, defined as no vomiting, no rescue, and no significant nausea and a numeric rating scale value of 0 to 2; total control rates, defined as no vomiting, no rescue, and no significant nausea and a numeric rating scale value of 0; and AEs.

Thirty patients were enrolled from May 2015 through October 2015. Patients had a median age of 64 years (range, 36-75 years), and 77% were male. Tumor types included non-small

cell lung cancer (63.3%), small cell lung cancer (26.7%), malignant pleural mesothelioma (6.7%), and thymoma (3.3%). The majority of patients received cisplatin-based treatment as part of systemic chemotherapy (63.3%) or chemoradiation (30.0%), with 6.7% of patients receiving it as postoperative adjuvant therapy. Most patients received cisplatin at 75 mg/m² (46.7%) or 80 mg/m² (40.0%), with 13.3% receiving a dose of 60 mg/m². Cisplatin was most commonly administered in combination with pemetrexed (46.7%), etoposide (23.3%), or vinorelbine (13.3%).

The olanzapine combination yielded a CR rate of 83% in the overall phase, meeting its primary endpoint. In the acute and delayed phases, the CR rates were 100% and 83%, respectively. The complete control rates in the acute, delayed, and overall phases were 93%, 73%, and 70%, respectively (Table 4). The total control rates in the acute, delayed, and overall phases were 77%, 70%, and 63%. No grade 3 or 4 AEs occurred during treatment, and no patients discontinued olanzapine treatment. Four patients (13%) experienced grade 1 somnolence, an AE commonly observed in patients treated with olanzapine.

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Nausea as a Symptom Cluster

Therapies introduced during the last decade have alleviated the majority of chemotherapy-associated vomiting.^{1,2} To combat CINV associated with HEC, guidelines recommend triple-therapy combinations that include a 5-HT₃ receptor antagonist, dexamethasone, and an NK₁ receptor antagonist. Although these combinations are effective in reducing emesis, nausea continues to be a concern for a large proportion of patients.

In a symposium focused on nausea, Dr Ian Olver presented an overview of studies revealing that patients use the term “nausea” to describe a wide range of symptoms, and that treatments addressing these broader symptoms may be needed to increase efficacy.³ Nausea has been described as “an unpleasant feeling that is usually accompanied by changes in autonomic nervous system activity, particularly (but not exclusively) the parasympathetic division.”⁴ Up to 75%

of patients undergoing chemotherapy will report nausea at some point, and many patients continue to experience anticipatory or conditioned nausea years after the cessation of chemotherapy treatment.⁵

In a qualitative study of 17 patients who experienced nausea during chemotherapy, patients described their experience as distressing and complex.⁶ Patients attempted to understand their symptoms by analyzing their own experience of nausea and related symptoms, attributing causation to nausea, and comparing their own experiences with those of others and with their own expectations. Concurrent symptoms included sleep disturbance, fatigue, bloating, sore throat, sweating, weakness, dizziness, headache, flu-like symptoms, and feeling hot and cold. Combinations of these symptoms were present when nausea arose.

CINV negatively impacts quality of life, as described in a longitudinal

secondary analysis of data derived from a prospective, observational study of 200 newly diagnosed cancer patients who underwent combined modality treatment.⁷ Quality of life, psychological adjustment, and patient and clinical characteristics were examined before treatment, during 8 weeks of treatment, and after treatment. Nausea was more than twice as common as vomiting, with 62% and 27% of patients reporting the symptoms, respectively. Quality-of-life scores yielded a recurrent gastrointestinal symptom cluster consisting of nausea, vomiting, and loss of appetite, with approximately two-thirds of patients reporting these symptoms concomitantly. This symptom cluster was accompanied by reductions in physical and social functioning; increased fatigue, nausea and vomiting; loss of appetite; increased psychological distress; and decreases in overall physical health and quality of life. The symptom cluster resulted in reduced quality of life for affected patients compared with unaffected patients. In a study of 16 breast cancer patients who had completed chemotherapy, patients tended to describe nausea as an ache or unsettled feeling in the stomach or throat or as feeling the need to vomit.⁸

A study was conducted to further elucidate whether patients’ experience of nausea in fact represents a cluster of symptoms.⁹ Patients with current or past experience of chemotherapy-induced nausea were interviewed. Each group of patients consisted of 12 women and 9 men. Study participants had a median age of 50 years, and were a median 3.5 years past treatment. Current patients had a median age of 54 years, and were treated in an outpatient clinic. Across both patient groups, the nature, number, location, duration, and intensity of experiences described as nausea varied, and no

ABSTRACT SUMMARY Effects of Rolapitant Administered Intravenously on the Pharmacokinetics of Cooperstown Cocktail (Midazolam, Omeprazole, Warfarin, Caffeine, and Dextromethorphan) in Healthy Volunteers

An open-label drug-drug interaction study was undertaken to evaluate the effects of IV rolapitant on the pharmacokinetics, safety, and tolerability of Cooperstown cocktail, which includes midazolam (CYP3A4), omeprazole (CYP2C19), S-warfarin (CYP2C9), caffeine (CYP1A2), and dextromethorphan (CYP2D6), in healthy volunteers (Abstract 0492). The 36 subjects received the oral Cooperstown cocktail on days 1, 7, and 14, IV rolapitant (166.5 mg) on day 7, and dextromethorphan alone on days 21, 28, and 35. IV rolapitant had no effects on the pharmacokinetics of S-warfarin or caffeine. As observed in studies of oral rolapitant, IV rolapitant had minimal and clinically nonsignificant effects on the pharmacokinetics of midazolam and omeprazole. IV rolapitant affected dextromethorphan pharmacokinetics, with the greatest impact observed 14 days after administration of IV rolapitant for both C_{max} (GMR, 2.74; 90% CI, 2.21-3.40) and AUC (GMR, 3.36; 90% CI, 2.74-4.13). No clinically significant AEs or laboratory results were reported. However, the authors recommended monitoring patients for safety parameters if concomitant use of IV rolapitant and dextromethorphan substrates is required.

single symptom was common to all descriptions. Physical and psychological symptoms included dry retching, vomiting, loss of appetite, indigestion, change of taste, dizziness, bloating, reflux, inability to concentrate, fatigue, and physical restlessness. Onset ranged from immediate to the fifth day after chemotherapy. The duration of nausea ranged from 1.5 hours to 6 months; however, conditioned stimuli could trigger nausea for years after cessation of treatment. For most patients, chemotherapy-induced nausea was distinguished from other experiences of nausea by several factors, including its constant presence over time, emotional associations with the cancer diagnosis, and the concomitant presence of fatigue. Nausea often had a negative impact on social and work interactions. Antiemetic agents reduced the intensity of nausea but did not fully alleviate it. Preferred management techniques included relaxation and distractions, such as working and watching television.

Most physical sensations involved the stomach, with descriptions of pressure or feeling full, feelings of queasiness or churning, or feeling that the stomach was rejecting food. Nausea affected patients' eating patterns and appetite. Many patients experienced swallowing difficulties tied to sensations of the throat constricting, and others experienced taste alterations that made food undesirable, whereas 2 patients reported increased appetite. Other physical sensations included whole body fatigue, restlessness, dizziness, and fever. The psychological symptoms led to added distress because they provided a constant reminder of the cancer. The findings suggest that more effective treatment of nausea may require treatment of the component symptoms by more judicious use of drugs, including olanzapine, cannabinoids, and antacids, but also through nonpharmacologic approaches, such as changes to the diet and determining which distractions are most effective.

A meta-analysis of olanzapine was conducted to assess the efficacy of olanzapine for the prevention of CINV after MEC or HEC.¹⁰ The analysis included 6 studies involving a total of 726 patients, of whom 441 were Chinese. The authors concluded that for the overall and Chinese populations, regimens containing olanzapine are more effective at reducing CINV than regimens that do not contain olanzapine, particularly in the delayed phase.

In addition to underscoring the need to develop more effective drugs, Dr Olver described development of a patient-reported outcomes tool, ePRO, to identify and assess components of the larger nausea symptom cluster during chemotherapy. Use of the tool could enable treatment of patients on a personalized basis by targeting specific symptoms. Other potential uses for the ePRO tool include assessment of pretreatment risk factors to guide prophylactic treatment and to reduce anticipatory nausea in cancer survivors.

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ABSTRACT SUMMARY Results of a Survey of Oncology Nurses Assessing Practice Patterns for Prevention of Chemotherapy-Induced Nausea and Vomiting (CINV) and Adherence to Antiemetic Guidelines

An online survey of oncology nurses was conducted to evaluate awareness of antiemetic guidelines and to assess current practice patterns in the administration of antiemetic therapies (Abstract 0452). Approximately 8000 practicing oncology nurses in the United States were invited to participate in the survey. Among the 531 nurses who completed the survey, most were full-time, oncology-certified staff nurses working in the outpatient setting. Of the surveyed nurses, 73% were familiar with National Comprehensive Cancer Network guidelines, and 48% were familiar with those of the American Society of Clinical Oncology. Only 6% cited familiarity with MASCC guidelines. In the HEC setting, NK₁ receptor antagonists were used on day 1 by 81% of respondents, and 5-HT₃ receptor antagonists were used by 78% of respondents on day 2 and beyond. In the MEC setting, dexamethasone was underutilized, with 89% of respondents reporting use on day 1 and 61% reporting use on day 2 and beyond. Use of phenothiazines and benzodiazepines on day 2 and beyond, which contradicts guidelines, was reported by 47% and 30% of respondents, respectively. Physician preference was cited as the greatest barrier interfering with administration of guideline-recommended prophylactic treatment by oncology nurses in both the HEC and MEC settings (71% and 70%, respectively). The greatest challenges cited by respondents were controlling CINV in the delayed phase and the effect of CINV on patient quality of life.

Highlights in CINV From the 2016 MASCC/ISOO Annual Meeting: Commentary

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The 2016 annual meeting of the Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology was held on June 23 to 25 in Adelaide, Australia. Several studies were presented in the field of chemotherapy-induced nausea and vomiting (CINV), with a focus on the newer antiemetic agents. Data were presented from new trials, subanalyses of pivotal trials, and retrospective studies.

In the last 2 years, the US Food and Drug Administration approved 2 new agents for CINV. Before these approvals, CINV management generally consisted of a 5-hydroxytryptamine 3 (5-HT₃) receptor antagonist and dexamethasone. Both of the new agents are neurokinin 1 (NK₁) receptor antagonists. NEPA is a fixed-dose oral combination of netupitant, a new NK₁ receptor antagonist, and palonosetron, a second-generation 5-HT₃ receptor antagonist. NEPA was approved in 2014. Rolapitant, a new NK₁ antagonist, was approved in 2015. Rolapitant is long-acting and has no known interactions with cytochrome P450 (CYP450), in contrast to previous NK₁ antagonists. In practice, CYP450 interactions require dose adjustment of other medications, such as dexamethasone. Many of the CINV studies at MASCC presented trial data for rolapitant and NEPA.

Studies of Rolapitant

The largest group of studies evaluated rolapitant. Several of the abstracts presented post hoc subgroup analyses

derived from the pivotal phase 3 trials that proved the benefit of rolapitant, as defined by complete response rates and other secondary endpoints. In these trials, patients were randomly assigned to receive the 5-HT₃ receptor granisetron plus dexamethasone, with either rolapitant (180 mg orally) or placebo. Two of these trials were conducted in patients receiving highly emetogenic chemotherapy (HEC) regimens that included cisplatin.¹ The third trial enrolled patients receiving moderately emetogenic chemotherapy (MEC) that included anthracycline and cyclophosphamide (AC).² At the time this trial was designed, AC was considered MEC. Subsequently, it was recognized that the specific AC combination has emesis potential in the high range (90%+), and the combination was reclassified as HEC. Approximately half of the patients received AC and the other half received other MECs, including carboplatin.

Dr Lee Schwartzberg presented results from a post hoc subgroup analysis of the rolapitant phase 3 trial of patients receiving MEC,² focusing on the breast cancer population.³ The phase 3 trial included 1332 patients, of whom 845 had breast cancer. As in the overall population, approximately half of the breast cancer patients received AC and the other half received other MECs, including carboplatin. The subgroup analysis showed superior control of CINV with rolapitant during the delayed phase and the overall phase, which is the 5-day period after administration of chemotherapy. In terms of secondary endpoints, there

was also an improvement in emesis.

We learned from this study that CINV occurred in approximately half of the patients who received a 2-drug combination of a 5-HT₃ receptor antagonist and dexamethasone. Rolapitant improved control of CINV by 8% to 10%. The incidence of adverse events was low and similar in the rolapitant and active-control arms. There is still an unmet need in breast cancer patients for control of nausea after MEC or AC-based chemotherapy.

Dr Rudolph Navari presented an analysis of the lung cancer patients from the HEC and MEC phase 3 trials.^{1,2,4} This analysis included 687 patients, who received treatment with carboplatin or cisplatin. (Eight patients received treatment with other MECs, AC, or no chemotherapy, and were excluded from this analysis.) In the HEC trials, most of the patients who received cisplatin had lung cancer. Again, rolapitant improved the complete response rate very substantially, by more than 12% in the overall and delayed phases. In addition, rolapitant was associated with clinical and statistical improvements in other secondary endpoints, such as no emesis, no nausea, and complete protection.

A third subanalysis, on gynecologic oncology patients, was presented by Dr Bernardo Rapoport.⁵ Among the 201 patients in this subgroup, approximately half had received cisplatin and the other half carboplatin. The addition of rolapitant improved complete response rates in the delayed and overall phases by approximately 15% compared with granisetron and dexamethasone alone.

There was also an improvement in no emesis, no nausea, and complete protection against CINV.

Another post hoc analysis by Dr Rudolph Navari focused on how well rolapitant controls nausea.⁶ Treatment of nausea remains an unmet need, even with the introduction of excellent therapies, such as the NK₁ agents. In the 3 pivotal trials, the addition of rolapitant improved the aggregated rates of patients without nausea.^{1,2} Rolapitant also improved the ability of patients to function while they had nausea, as assessed by the Functional Living Index-Emesis (FLIE) questionnaire, a validated tool that patients completed daily for 5 days after receiving chemotherapy.

Dr Matti Aapro analyzed data from the phase 3 rolapitant trials according to age.⁷ It has been known for many years that younger patients tend to develop more CINV. In this analysis, age 65 years was the cutoff. The analysis also considered the use of AC vs other agents. Rolapitant had a good benefit in both the younger and older patients. Older patients treated with AC were less susceptible to developing CINV than the younger patients. Interestingly, among patients in the control arm who received the highly emetogenic agent cisplatin, rates of CINV did not differ substantially between the patients who were younger vs older. Rolapitant improved the complete response rate in younger and older patients in similar increments.

There were several pharmacokinetic studies of rolapitant. Dr Xiaodong Wang, a pharmacologist, presented results from a study that compared oral vs intravenous (IV) administration of rolapitant in healthy volunteers.⁸ The oral dose was 180 mg, and the IV dose was given as a 30-minute infusion of 166.5 mg. The study found that the pharmacokinetics of the doses were very similar, and the systemic exposure was equivalent. A follow-up study evaluated supratherapeutic doses of rolapitant that reached 270 mg, which is up to 1.5 times the standard

dose.⁹ The pharmacokinetics were dose proportional; that is, there was an expected increase in exposure that was relative to the actual dose. Importantly, there was no additional or significant toxicity with the higher dose.

The potential for rolapitant to act on P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) substrates prompted a drug-drug interaction study presented by Dr Jing Wang.¹⁰ Some chemotherapeutic agents are potential substrates for P-gp and BCRP, and might interact with them. This analysis evaluated IV rolapitant. A previous study of oral rolapitant had shown no interaction. The study by Dr Jing Wang found no major effect of IV rolapitant on the pharmacokinetics of the P-gp substrate digoxin or the BCRP substrate sulfasalazine. No dose adjustments were deemed necessary.

Studies of NEPA and Palonosetron

Several studies evaluated NEPA. Dr Petra Feyer presented preliminary results from a large survey study conducted in Germany of patients

who received NEPA in the setting of HEC or MEC.¹¹ Data concerning CINV are being gathered through patient self-assessment on the FLIE questionnaire and physician surveys. The study is expected to accrue more than 2000 patients. This preliminary analysis provided results for 583 of the 700 patients recruited so far. The vast majority of patients were female, and 70% had breast cancer. The treatment regimens included AC in 56% and carboplatin in 18%.

The clinicians judged the efficacy of NEPA as good or very good in more than 90% of patients. The complete response rates were remarkable, at 85.1% for the delayed phase and 79.3% for the overall phase. The emesis rates were remarkably low, with control rates consistently over 90%. This study provides real-world data showing extremely good control with NEPA and dexamethasone in MEC and HEC.

Dr Matti Aapro presented a drug-drug interaction study evaluating whether there was increased toxicity when NEPA was given with docetaxel or etoposide.¹² Netupitant is known to have an inhibitory effect on cytochrome P450 isoenzyme 3A4

ABSTRACT SUMMARY Managing Chemotherapy-Induced Nausea and Vomiting (CINV) in Head and Neck Cancer Patients Receiving Cisplatin Chemotherapy With Concurrent Radiation

A retrospective study of patients with head and neck cancer receiving cisplatin-based chemotherapy and concurrent radiation was conducted to determine patterns of CINV and to assess changes made to antiemetic therapy in subsequent treatment cycles (Abstract 0122). The analysis included a consecutive cohort of patients receiving high-dose cisplatin every 3 weeks (n=161) or low-dose cisplatin every week (n=38) with concurrent radiation between January 2013 and June 2015. In the high- and low-dose cisplatin cohorts, nausea and/or vomiting occurred in 85% and 60% of patients, respectively, during cycle 1 and in 14% and 20% of patients during cycle 2. Among patients who experienced CINV, changes to antiemetic therapies were made in only half of the high-dose arm and two-thirds in the low-dose arm. In most patients, modification of the antiemetic regimen consisted of changes to the 5-HT₃ receptor antagonist—either a dose extension or a switch to a different agent. Other changes to antiemetic therapy included changes to breakthrough antiemetics and changes to dexamethasone dosing.

(CYP3A4).¹³ This pooled safety analysis included data from 4 studies. There was some increase in exposure to chemotherapy owing to the effect of NEPA on CYP3A4, but no change in toxicity. It was therefore safe to administer NEPA in patients receiving docetaxel or etoposide without any dose adjustments.

Dr Michiko Tsuneizumi presented the results of a phase 3 trial that compared palonosetron vs granisetron, both in combination with the NK₁ receptor antagonist aprepitant and dexamethasone.¹⁴ Palonosetron, a component of NEPA, has shown superiority over a first-generation 5-HT₃ receptor antagonist when given in a 2-drug combination with dexamethasone.¹⁵ This study enrolled nearly 500 patients. It found that palonosetron was associated with numeric improvements as compared with granisetron in the treatment of CINV in the delayed and overall phases, but the differences did not reach statistical significance.

Studies in Olanzapine

Olanzapine is a multi-neuroreceptor targeted drug that inhibits several dopamine receptors, as well as other types. There has been great interest in olanzapine as an adjunctive drug in CINV. It is being evaluated as an addition to the current triplet regimen for patients who require maximal prophylaxis against CINV, as a substitute for an NK₁, and as a rescue medication for patients who develop breakthrough CINV. Phase 3 studies have shown similar results when olanzapine replaces an NK₁ receptor antagonist.

Kouichi Yokoyama presented results from a small, phase 2 study of a 4-drug combination in patients with thoracic malignancies.¹⁶ Olanzapine, given at 5 mg/day for 5 days after the administration of platinum-based chemotherapy, was added to treatment with palonosetron, aprepitant, and dexamethasone. The study evaluated

rates of total control, an endpoint indicating no vomiting, emesis, or nausea. The overall total control rate was 63%, which was good.

A retrospective study evaluated the use of olanzapine at a hospital system based on pharmacy records.¹⁷ There were 2 groups of patients. The larger group used olanzapine for breakthrough CINV, and a smaller group used olanzapine in the prophylactic setting. The study found that the addition of olanzapine improved breakthrough CINV in 87% of patients. The patients who received olanzapine as prophylactic treatment also had improved control of CINV. As expected, sedation was the major side effect of olanzapine.

Nausea

The MASCC meeting included a symposium on nausea.¹⁸ There is increasing recognition in the CINV community that nausea represents the major remaining unmet need in CINV management, and it is a substantial one. This need is particularly acute for certain chemotherapies, such as AC. Although nausea is related to vomiting, it is a purely subjective finding, making it more difficult to measure. Triggers of nausea may utilize alternative neurologic and gastrointestinal pathways compared with vomiting.

The speakers at the symposium suggested that future attention will be placed on control of nausea and evaluating nausea as a primary endpoint. The traditional endpoint in clinical trials, complete response rate, is defined as no emesis. To some extent, this endpoint is a clinical trial construct and used because it can be easily measured objectively. Another common endpoint, no use of rescue medication, is subjective and variable depending on the study design. Going forward, the aim is for trials to incorporate more stringent endpoints, such as no significant nausea or no nausea, because the goal is to prevent any CINV symptoms whatsoever.

Disclosure

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