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Rolapitant for the Prevention of Nausea in Patients Receiving Cisplatin- or Carboplatin-Based Chemotherapy: Alternative Methods for Evaluating Nausea

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BACKGROUND

- Rolapitant (VARUBI®) is a selective and long-acting neurokinin 1 (NK-1) receptor antagonist approved in the United States in adults for the prevention of chemotherapy-induced nausea and vomiting (CINV).[1]
  - The intravenous formulation of rolapitant is currently under review by the FDA.
- In global randomized phase 3 trials of patients receiving cisplatin- and carboplatin-based chemotherapy, the addition of a single oral 180-mg dose of rolapitant to a standard antiemetic regimen of a 5-hydroxytryptamine type 3 receptor antagonist (5-HT_3 RA) and dexamethasone significantly improved protection against CINV during the delayed phase (>24–120 hours post chemotherapy).[2,3]
- Traditional assessments of nausea do not consider the use of rescue medications (RMs).
- RMs might mask nausea symptoms, precluding accurate evaluation of the efficacy of nausea prevention.

OBJECTIVES

- An exploratory post hoc analysis was conducted to evaluate the contribution of rolapitant in reducing nausea duration and to assess nausea in the absence of rescue medication.

METHODS

- Post hoc analyses of nausea were performed using results from three global, randomized, double-blind phase 3 studies that enrolled patients naïve to cisplatin-based chemotherapy (pooled data from NCT01499849 and NCT01500213; rolapitant, n=535; control, n=535) or carboplatin-based chemotherapy (NCT01500226; rolapitant, n=192; control, n=209).
- Patients were stratified by sex and randomized (1:1) to receive either 180 mg oral rolapitant + 5-HT_3 RA + dexamethasone or matched placebo + 5-HT_3 RA + dexamethasone approximately 1-2 hours before chemotherapy administration on day 1.
- Patients self-assessed nausea for 5 days following chemotherapy using a 100-mm visual analogue scale (VAS) to indicate severity. The percentages of patients with no nausea (maximum VAS <5 mm) and no significant nausea (VAS <25 mm) were calculated for all phases of CINV in cycle 1.
  - The percentage of patients with No Nausea or No Significant Nausea and who did not use RMs were assessed by chemotherapy administered (cisplatin-based or carboplatin-based) in all phases. Nausea duration (measured by assessing the number of days with nausea) was also evaluated.
- *P* values <0.05 were considered statistically significant and were not adjusted for multiplicity.

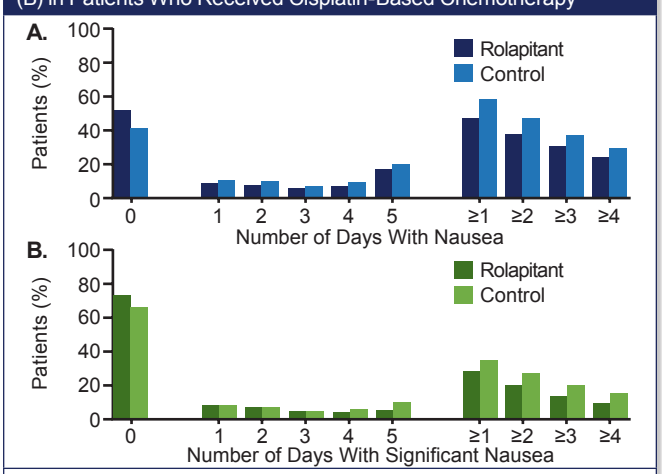
RESULTS

Table 1. Patient Demographics and Baseline Characteristics

Characteristic	Cisplatin-Based		Carboplatin-Based	
	Rolapitant (n=535)	Control (n=535)	Rolapitant (n=192)	Control (n=209)
Age, y				
Median	59	59	61	64
Min, max	(21, 86)	(18, 90)	(31, 83)	(23, 88)
Age ≥65 y, n (%)	138 (25.8)	142 (26.5)	68 (35.4)	98 (46.9)
Female, n (%)	198 (37.0)	199 (37.2)	104 (54.2)	116 (55.5)
Receipt of concomitant emetogenic chemotherapy, n (%)[a]				
Yes	87 (16.3)	101 (18.9)	26 (13.5)	37 (17.7)

[a]Patients received at least one Hesketh level ≥3 agent in addition to either cisplatin-based or carboplatin-based chemotherapy.

Figure 1. Number of Days With Nausea[a] (A) and Significant Nausea[b] (B) in Patients Who Received Cisplatin-Based Chemotherapy



[a]Maximum VAS ≥5 mm on a 0–100 mm scale. [b]VAS ≥25 on a 0–100 mm scale. VAS=visual analogue scale.

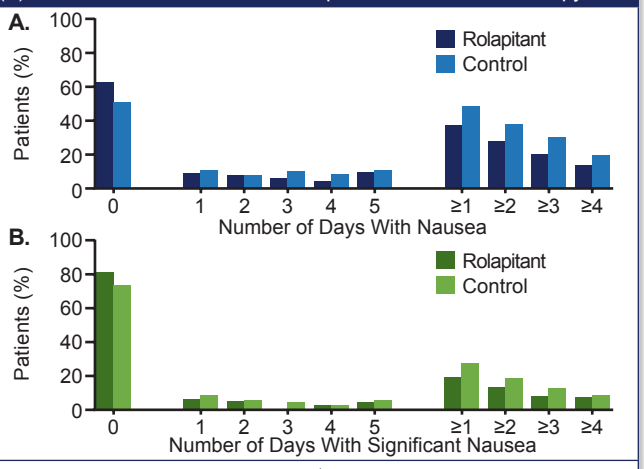
- In patients receiving cisplatin-based chemotherapy, No Nausea during the overall phase (0 days with nausea) was observed in 52.3% with rolapitant vs 41.7% with control, and No Significant Nausea during the overall phase (0 days with significant nausea) was observed in 72.1% with rolapitant vs 65.4% with control.
- In patients receiving carboplatin-based chemotherapy, No Nausea during the overall phase (0 days with nausea) was observed in 62.5% with rolapitant vs 51.2% with control, and No Significant Nausea during the overall phase (0 days with significant nausea) was observed in 80.7% with rolapitant vs 72.7% with control.

Table 2. Percent of Patients With No Rescue Medication Use and No Significant Nausea or No Nausea by CINV Phase

Parameter	Cisplatin-Based				
	Rolapitant (n=535)	Control (n=535)	Absolute Benefit,[a] %	NNT[b]	*P*[c]
No RM use, %					
Overall phase	81.9	73.8	8.1	12	0.002*
Delayed phase	82.8	75.5	7.3	-	0.003*
Acute phase	93.3	86.7	6.6	-	<0.001*
No RM use + No Significant Nausea,[d] %					
Overall phase	67.7	60.2	7.5	13	0.011*
Delayed phase	69.9	61.7	8.2	-	0.005*
Acute phase	85.6	78.5	7.1	-	0.002*
No RM use + No Nausea,[e] %					
Overall phase	51.0	41.1	9.9	10	0.001*
Delayed phase	54.6	43.6	11.0	-	<0.001*
Acute phase	69.0	63.0	6.0	-	0.038*
Parameter	**Carboplatin-Based**				
	Rolapitant (n=192)	Control (n=209)	Absolute Benefit,[a] %	NNT[b]	*P*[c]
No RM use, %					
Overall phase	82.3	71.8	10.5	10	0.013*
Delayed phase	83.9	72.7	11.2	-	0.007*
Acute phase	94.3	89.5	4.8	-	0.081
No RM use + No Significant Nausea,[d] %					
Overall phase	74.5	65.1	9.4	11	0.041*
Delayed phase	76.6	66.0	10.6	-	0.020*
Acute phase	89.1	87.1	2.0	-	0.542
No RM use + No Nausea,[e] %					
Overall phase	60.4	48.3	12.1	8	0.015*
Delayed phase	63.0	51.2	11.8	-	0.017*
Acute phase	79.7	75.6	4.1	-	0.327

Overall phase: 0–120 h, delayed phase: >24–120 h, acute phase: ≤24 h. [a]% difference (rolapitant minus control). [b]NNT=1/absolute benefit; the number of patients needed to treat with rolapitant to observe a benefit in one patient. [c]*P* values obtained from the Cochran-Mantel-Haenszel χ^2 test, stratified for sex and study, for the pooled cisplatin-based studies; * indicates statistical significance (*P*<0.05). [d]VAS <25 on a 0–100 mm scale. [e]VAS <5 mm on a 0–100 mm scale. CINV=chemotherapy-induced nausea and vomiting; NNT=number needed to treat; RM=rescue medication; VAS=visual analogue scale.

Figure 2. Number of Days With Nausea[a] (A) and Significant Nausea[b] (B) in Patients That Received Carboplatin-Based Chemotherapy



[a]Maximum VAS ≥5 mm on a 0–100 mm scale. [b]VAS ≥25 on a 0–100 mm scale. VAS=visual analogue scale

CONCLUSIONS

- The addition of rolapitant to a standard antiemetic regimen of a 5-HT_3 RA and dexamethasone reduced nausea incidence and RM use in patients receiving cisplatin- or carboplatin-based chemotherapy.
- Patients receiving rolapitant + 5-HT_3 RA + dexamethasone experienced fewer days with nausea than patients receiving placebo + 5-HT_3 RA + dexamethasone.
  - Assessing the number of days with nausea is a novel alternative method for quantifying nausea.
- The clinical benefit of rolapitant administration was similar regardless of RM use, therefore the use of RM does not confound the analysis of nausea.[2,3]

REFERENCES

1. VARUBI® (rolapitant) [prescribing information]. Waltham, MA: TESARO, Inc.; 2015.
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