

Update on the management of chemotherapy-induced nausea and vomiting – focus on palonosetron

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Purpose: Nausea and vomiting are major adverse effects of chemotherapy and can greatly impact patients' quality of life. Although chemotherapy-induced nausea and vomiting (CINV) prevalence is high, treatment remains difficult. Palonosetron is a 5-hydroxytryptamine receptor antagonist (5-HT₃RA) approved for treatment of CINV. The purpose of this review is to discuss existing and emerging therapeutic options, and examine studies focusing on palonosetron with regards to efficacy, pharmacology, tolerability, safety, and patient-derived outcomes.

Methods: A literature search was conducted using Ovid MEDLINE and EMBASE to identify relevant studies using palonosetron alone or in combination with other antiemetics. Studies were extracted if they included complete response (CR), complete control (CC), no nausea, no vomiting, and no rescue medications as an endpoint. Studies were also included if safety endpoints were examined.

Results: Palonosetron alone has been shown to improve CR and CC rates for patients receiving low, moderate, or high emetogenic chemotherapy. Rates were further improved with the addition of dexamethasone, a corticosteroid. Furthermore, the addition of neurokinin-1 receptor antagonists, such as netupitant markedly improved efficacy profiles compared to palonosetron alone. Aprepitant is an antiemetic that has exhibited positive results in combination with palonosetron. Recently, a new drug consisting of netupitant and palonosetron (NEPA) has demonstrated significantly more efficacious prevention of CINV. Regardless of the combination, palonosetron has been well tolerated. The most common adverse events were constipation, headache, fatigue, and dizziness, with the majority of patients describing them as only mild or moderate.

Conclusion: Palonosetron, alone or with other antiemetics, has improved CINV treatment due to its ability to significantly reduce delayed phases of CINV, compared to similar 5-HT₃RAs. Palonosetron is both more effective than first generation 5-HT₃RAs and safer, as it results in a smaller prolongation of the QTc interval, compared to other 5-HT₃RAs.

Keywords: chemotherapy-induced nausea and vomiting, palonosetron, efficacy, safety, pharmacology, patient-reported outcomes

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is considered a major adverse effect of cytotoxic chemotherapy and can greatly impact patients' quality of life.¹⁻³ As a result, CINV is one of the major reasons for disruption or delay in treatment, which is often due to patient noncompliance.³ The administration of a safe and efficacious prophylactic antiemetic regimen is thus important for current and future patients at risk for CINV.⁴ In antiemetic clinical trials, there are five common endpoints that are employed for comparison: complete response (CR), defined as no emesis and no use

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of rescue medication; complete control (CC), defined as CR with the addition of no mild nausea; no emetic episodes; no episodes of nausea; and no use of rescue medication.⁴

Trials that used first generation 5-hydroxytryptamine receptor antagonists (5-HT₃RA), including ondansetron, granisetron, tropisetron, and dolasetron, concluded that, although they were successful in controlling the rates of vomiting, nausea still remained a concern, especially in the delayed phase.⁴ The addition of dexamethasone to 5-HT₃RA is highly effective for acute emetic control; however, the effect on delayed emesis is less evident.⁵ Despite the introduction of more effective antiemetic agents, nausea and vomiting remain a significant complication of chemotherapy.¹

Mechanism of CINV

CINV is composed of an acute phase and delayed phase. The acute phase is defined as nausea and vomiting occurring 0–24 hours after administration of chemotherapy, whereas the delayed phase occurs between 24 hours and up to 5 days later.⁶

Different but overlapping pathological pathways are involved in the pathogenesis of CINV.³ The emetic center is believed to be a loosely organized network of neurons in the medulla oblongata.³ Chemotherapy agents are thought to activate the release of neurotransmitters, in particular, serotonin, which activates vagal afferents leading to stimulation of the area postrema. Sensory inputs in vagal afferents and the area postrema are then consolidated at the emetic center, resulting in efferent signals that lead to contraction of abdominal muscles, the diaphragm, stomach, and esophagus, producing a reflexive emetic response.³ Several neurotransmitters are thought to be involved in this process and include dopamine, serotonin (5-HT), and substance P (SP). As a result, drugs that antagonize the action of these neurotransmitters have been developed as prophylactic therapies for CINV.³

Emerging and existing treatments

Early treatments of CINV involved the use of dopamine D₂ receptor antagonists, the most common of which is metoclopramide.¹ Some believe that the antiemetic effects of metoclopramide are due to its weak inhibition of 5-HT₃ receptors (which is achieved when it is administered at high doses).¹

Chemotherapy can also induce the release of SP, which acts on neurokinin-1 (NK-1) receptors located both peripherally and centrally.^{6,7} NK-1 receptor antagonists (NK-1 RAs) have been developed to prevent both acute and delayed CINV.⁷ The broad spectrum of antiemetic activity allows these medications to control many forms of induced

emesis.⁸ Aprepitant was the first approved NK-1 RA whereas others, like netupitant, are still undergoing clinical trials.⁵ Previous guidelines for CINV management have recommended NK-1 RAs for prophylaxis of delayed phases of CINV due to highly (HEC) or moderately emetogenic chemotherapy (MEC).⁷

Enterochromaffin cells located in the small intestine release serotonin which binds to 5-HT₃ receptors on vagal afferents.⁴ Throughout the 1990s, several 5-HT₃RA including ondansetron, granisetron, tropisetron, and dolasetron were introduced as antiemetic agents.^{1,4} These agents bind to the same binding site as serotonin on the 5-HT₃ receptor, and, as a result, the CINV effects normally produced by the vagal afferents are inhibited.¹

Typically, 5-HT₃RA alone are used for the treatment of acute-phase emesis, whereas both acute and delayed phases are treated with NK-1 RAs in conjunction with 5-HT₃RA and dexamethasone. A number of international groups have suggested that prior to chemotherapy, a combination of 5-HT₃RA and dexamethasone be used for acute CINV prophylaxis.¹ However, postchemotherapy, dexamethasone should be used alone for delayed CINV prophylaxis.¹

A new 5-HT₃RA known as palonosetron (Aloxi®, Helsinn Healthcare SA, Pazzallo, Switzerland) was developed to improve response rates, and was approved by the US Food and Drug Administration for delayed emesis treatment.⁹ Palonosetron is a second-generation 5-HT₃RA that has a uniquely strong binding affinity for the serotonin receptor.¹⁰ Studies have shown that palonosetron can reduce the incidence of delayed CINV through inhibition of SP, which is not evident in certain first generation 5-HT₃RA.¹¹ The purpose of this review is to examine published data on palonosetron with regard to efficacy, pharmacology, tolerability, safety, and patient-derived outcomes.

Methods

A literature search was conducted using Ovid MEDLINE (1946 to August 2014 [Week 32]) and EMBASE (1947 to August 2014 [Week 32]). The following terms were combined in the search: “palonosetron” and “chemotherapy-induced nausea and vomiting”. Studies were screened for at least one of the following common endpoints: CR, CC, no nausea, no emesis, or no rescue medication. Studies were further stratified by inclusion of either acute or delayed phases. Another literature search was conducted using Ovid MEDLINE (2008 to August 2014 [Week 32]) and EMBASE (2008 to August 2014 [Week 32]) using the following search terms: “chemotherapy-induced nausea and vomiting” and

“antineoplastic agents” for articles that were relevant to the mechanism of CINV or antiemetic agents.

Results

A total of 818 articles from the literature search were examined for potential inclusion. The literature search as well as additional references from relevant review articles yielded 32 full articles. Of these, six articles discussed the pharmacology of palonosetron (Tables 1 and 2). Articles that included safety and efficacy were as follows: ten discussed palonosetron alone (Tables 3 and 4); ten discussed safety and efficacy of palonosetron in combination with dexamethasone; six discussed safety and efficacy of palonosetron in combination with aprepitant and dexamethasone; and two discussed safety and efficacy of NEPA (Tables 5 and 6).

Pharmacology

The summary of palonosetron pharmacokinetics can be found in Tables 1 and 2. Mean maximum plasma concentrations (C_{max}) and area under the concentration-time curve ($AUC_{0-\infty}$) generally increased in a dose-dependent manner.^{12,13} In 32 healthy American subjects, doses ranged from 0.3 to 90 $\mu\text{g/kg}$ giving rise to increases in both $AUC_{0-\infty}$ and C_{max} : 5.8–750 $\text{ng}\cdot\text{h/mL}$ and 0.114–23.9 ng/mL , respectively.¹² Similarly, Eisenberg et al¹³ reported the same trend in 35 cancer patients, with $AUC_{0-\infty}$ and C_{max} ranging from 13.8 to 957 $\text{ng}\cdot\text{h/mL}$ and 0.89 to 336 ng/mL , respectively, when given doses of 1–90 $\mu\text{g/kg}$ palonosetron.

Three studies involving healthy patients and one involving cancer patients found that total clearance (CL_T) for palonosetron was low.^{12–14} Additionally, volume of distribution (V_D) levels for both populations in all studies was found to be elevated, indicating high partitioning into tissue. At comparable doses of intravenous (IV) palonosetron, cancer patients exhibited lower mean CL_T and larger mean V_D values than their healthy counterparts. At a dose of 1 $\mu\text{g/kg}$, cancer patients recorded mean CL_T and V_D levels of 1.51 mL/min/kg and 12.5 L/kg , respectively, whereas healthy patients recorded mean values of CL_T = 1.89 mL/min/kg and V_D = 5.31 L/kg .^{12,13}

In both cancer and healthy populations, low CL_T and high V_D resulted in a longer half-life ($t_{1/2}$).^{12–16} The most extreme deviations in half-life from that noted by the manufacturer (ie, $t_{1/2}$ of approximately 40 hours) were exhibited by cancer patients; the greatest of which was reported to be $t_{1/2}$ = 128 hours, in a study with 161 cancer patients, while the shortest was $t_{1/2}$ = 12.71 hours.^{15,17}

Table 1 Study characteristics and pharmacokinetics of palonosetron in healthy subjects with no history of disease

Trial	Sample size	Dose	$AUC_{0-\infty}$ ($\text{ng}\cdot\text{h/mL}$)	C_{max} (ng/mL)	$t_{1/2}$ (h)	CL_T (mL/min/kg)	V_D (L/kg)
Stoltz et al ¹²	Study 1: n=80	0.3 $\mu\text{g/kg}$	5.8 \pm 3.46	0.114 \pm 0.063	54.1 \pm 36.6	1.11 \pm 0.652	3.85 \pm 0.645
		1 $\mu\text{g/kg}$	9.35 \pm 2.59	0.349 \pm 0.206	33.7 \pm 16.8	1.89 \pm 0.456	5.31 \pm 2.35
		3 $\mu\text{g/kg}$	29.8 \pm 9.02	0.918 \pm 0.250	47.2 \pm 14.7	1.81 \pm 0.547	6.88 \pm 0.874
		10 $\mu\text{g/kg}$	65.7 \pm 14.5	3.53 \pm 1.44	35.0 \pm 8.77	2.66 \pm 0.805	7.83 \pm 1.81
		20 $\mu\text{g/kg}$	153 \pm 44.1	5.71 \pm 2.93	37.0 \pm 6.15	2.36 \pm 0.766	7.27 \pm 1.19
		30 $\mu\text{g/kg}$	150 \pm 56.1	11.5 \pm 8.71	37.8 \pm 6.60	3.90 \pm 1.81	12.6 \pm 5.52
	Study 2: n=32	45 $\mu\text{g/kg}$	348 \pm 137	26.0 \pm 23.7	41.2 \pm 7.33	2.39 \pm 0.717	8.23 \pm 1.90
		60 $\mu\text{g/kg}$	370 \pm 70.1	17.1 \pm 4.37	41.8 \pm 9.55	2.78 \pm 0.488	9.78 \pm 1.17
		90 $\mu\text{g/kg}$	750 \pm 271	23.9 \pm 3.87	40.2 \pm 6.63	2.17 \pm 0.578	7.50 \pm 2.25
		3 $\mu\text{g/kg}$	15.2 \pm 4.58	4.68 \pm 4.68	30.8 \pm 9.22	3.50 \pm 0.817	8.81 \pm 1.38
		10 $\mu\text{g/kg}$	51.2 \pm 9.44	7.79 \pm 3.31	34.1 \pm 3.75	3.37 \pm 0.747	9.85 \pm 1.90
		30 $\mu\text{g/kg}$	208 \pm 68.3	23.3 \pm 3.13	31.3 \pm 3.55	31.3 \pm 0.667	6.96 \pm 1.75
Shah et al ¹⁵	15 minute infusion: n=11 30 minute infusion: n=11	90 $\mu\text{g/kg}$	561 \pm 129.0	52.6 \pm 36.7	36.8 \pm 4.72	36.8 \pm 0.549	8.70 \pm 1.24
		0.25 mg	17.5	0.919	37.0	Not specified	Not specified
		0.25 mg	17.7	1.65	33.3	Not specified	Not specified
Hunt et al ¹⁶	n=16	AUC_{0-24} ($\text{ng}\cdot\text{h/mL}$)		Day 1: 8.90 Day 3: 18.2	Day 1: 1.13 Day 3: 2.43	Not specified	Not specified

Note: Pharmacokinetic parameters are mean \pm standard deviation.

Abbreviations: AUC , area under the curve; C_{max} , maximum plasma concentration; h, hours; min, minutes; $t_{1/2}$, half-life; CL_T , total clearance; V_D , volume of distribution.

Table 2 Study characteristics and pharmacokinetics of palonosetron in cancer patients

Trial	Sample size	Dose	AUC _{0-∞} (ng·h/mL)	C _{max} (ng/mL)	t _{1/2} (h)	CL _T (mL/min/kg)	V _D (L/kg)
Eisenberg et al ¹³	n=161	1 µg/kg	13.8±7.58	0.055	128±93.8	1.51±0.70	12.5±4.19
		3 µg/kg	35.8±20.9	0.489	56.4±5.8	1.66±0.59	7.91±2.53
		10 µg/kg	81.8±23.9	0.141±0.104	49.8±14.4	2.23±0.83	9.56±4.21
		30 µg/kg	348±295	0.481±0.262	86.4±121	2.13±1.21	9.18±4.61
		90 µg/kg	957±450	0.855±0.679	43.7±12.2	1.90±0.82	6.83±2.67
Ikari et al ¹⁴	n=26	0.75 mg	Day 1: 76.0	Day 1: 2.05	Day 1: 39.4	CL _T (mL/min)	V _D (L)
			Day 3: 108.9	Day 3: 2.90	Day 3: 42.5	Day 1: 176	Day 1: 580
Sadaba et al ¹⁷	n=25	250 µg	Not specified	11.88±7.38	12.71±10.21	Not specified	Not specified

Note: Pharmacokinetic parameters are mean ± standard deviation.

Abbreviations: AUC, area under the curve; C_{max}, maximum plasma concentration; h, hours; min, minutes; n/a, not applicable; t_{1/2}, half life; CL_T, total clearance; V_D, volume of distribution.

Efficacy

Dose-ranging study

In 2003, Eisenberg et al¹³ conducted a dose-ranging study in patients receiving HEC to determine the efficacy and safety of palonosetron. A total of 161 patients were enrolled, with doses ranging from 0.3 to 90 µg/kg. Overall,

those that received lower doses of palonosetron exhibited a lesser response to therapy than those that received higher doses. Within the first 24 hours, most patients receiving elevated doses (ie, 3, 30, and 90 µg/kg) experienced less nausea, and did not require rescue medication. CRs were exhibited in approximately 50% of the patients for each

Table 3 Study design and characteristics of patient population in palonosetron-only studies

Study	Phase	Intervention	Sample size	Chemotherapy emetogenicity	Mean age, years
Eisenberg et al ¹³	n/a	1) Palonosetron 0.3–1.0 µg/kg 2) Palonosetron 3 µg/kg 3) Palonosetron 10 µg/kg 4) Palonosetron 30 µg/kg 5) Palonosetron 90 µg/kg	n=161	HEC	60
Hesketh et al ¹⁸	II	Palonosetron 0.25 mg IV	n=34	LEC	64.6
Di Renzo et al ⁹	II	Palonosetron 0.25 mg IV	n=86	MEC	n/a
Boccia et al ¹⁹	III	1) Palonosetron 0.25 mg oral	n=78	MEC	57.1 ^a
		2) Palonosetron 0.50 mg oral	n=82		56.1 ^a
		3) Palonosetron 0.75 mg oral	n=77		55.8 ^c
		4) Palonosetron 0.25 mg IV	n=81		57.7 ^a
Eisenberg et al ^{20,b}	III	1) Palonosetron 0.25 mg IV	n=189	MEC	53.3
		2) Palonosetron 0.75 mg IV	n=189		55.2
		3) Dolasetron 100 mg	n=191		53.6
Gralla et al ^{21,b}	III	1) Palonosetron 0.25 mg IV	n=189	MEC	56.1
		2) Palonosetron 0.75 mg IV	n=189		54.8
		3) Ondansetron 32 mg	n=185		55.3
Choi et al ²²	IV	1) Palonosetron 0.25 mg IV day 1 cycle 1	n=88	MEC	n/a
		2) Palonosetron 0.25 mg IV day 1 cycle 2	n=82		
		3) Palonosetron 0.25 mg IV day 1 cycle 3	n=78		
		4) Palonosetron 0.25 mg IV day 1 cycle 4	n=69		
Mattiuzzi et al ^{23,b}	n/a	1) Ondansetron 8 mg IV	n=47	HEC	n/a
		2) Palonosetron 0.25 mg IV from day 1 to day 5	n=48		
		3) Palonosetron 0.25 mg IV on days 1, 3, and 5	n=48		
Dong et al ^{24,b}	n/a	1) Palonosetron 0.25 mg IV	n=44	HEC	54
		2) Ondansetron 8 mg IV	n=45		52
Tian et al ^{25,b}	n/a	1) Palonosetron 0.25 mg IV	n=66	HEC or MEC	52.08 ^c
		2) Granisetron 3 mg IV	n=56		52.57 ^c

Notes: ^aThe baseline characteristics included those patients who had also received dexamethasone. This study was included in the dexamethasone and palonosetron combination section as well. ^bDenotes studies that compared palonosetron with first generation 5-HT₃ receptor antagonists. ^cThe baseline characteristics included patients who withdrew from the study before completion.

Abbreviations: 5-HT₃, 5-hydroxytryptamine; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; HEC, highly emetogenic chemotherapy; IV, intravenous; n/a, not applicable.

Table 4 Response rates and adverse events in palonosetron-only studies

Study	Intervention	CR – acute (%)	CC – acute (%)	CR – delayed (%)	CC – delayed (%)	Adverse events
Eisenberg et al ¹³	1) Palonosetron 0.3–1.0 µg/kg	24 ^a	Not specified. Only stated CC slightly lower than rates of CR	n/a	n/a	Headache (19.3%), constipation (8.7%), abdominal pain (2.5%), dizziness (2.5%)
	2) Palonosetron 3 µg/kg	46 ^a				
	3) Palonosetron 10 µg/kg	40 ^a				
	4) Palonosetron 30 µg/kg	50				
	5) Palonosetron 90 µg/kg	46 ^a				
Hesketh et al ¹⁸	Palonosetron 0.25 mg IV	88.2	85.3	67.6	64.7	Decreased appetite (5.6%), fatigue (5.6%), headache (5.6%), pyrexia (5.6%)
Di Renzo et al ⁹	Palonosetron 0.25 mg IV	90.7	89.5	88.4	84.9	Constipation (7.0%), headache (5.8%), asthenia (7.0%), dizziness (1.2%)
Boccia et al ^{19b}	1) Palonosetron 0.25 mg oral	70.1	n/a	61.0	n/a	Headache (3.7%–8.6%), constipation (0.6%–3.2%)
	2) Palonosetron 0.50 mg oral	66.7		61.7		
	3) Palonosetron 0.75 mg oral	62.8		56.4		
	4) Palonosetron 0.25 mg IV	57.5		62.5		
Eisenberg et al ²⁰	1) Palonosetron 0.25 mg IV	63.0 ^a	n/a	54.0	n/a	Headache (24.1%–26.8%), constipation (9.3%–14.9%), fatigue (10.9%–13.3%)
	2) Palonosetron 0.75 mg IV	57.1 ^a		56.6		
	3) Dolasetron 100 mg	52.9 ^a		38.7		
	1) Palonosetron 0.25 mg IV	81.0	n/a	74.1	n/a	Headache (4.8%–5.3%)
Gralla et al ²¹	2) Palonosetron 0.75 mg IV	73.5 ^a		64.6 ^a		
	3) Ondansetron 32 mg	68.6		55.1		
	1) Palonosetron 0.25 mg IV day 1 cycle 1	77.3	n/a	83.0	n/a	Constipation (2.3%), fatigue (1.1%)
Choi et al ²²	2) Palonosetron 0.25 mg IV day 1 cycle 2	84.1		93.9		
	3) Palonosetron 0.25 mg IV day 1 cycle 3	82.1		92.3		
	4) Palonosetron 0.25 mg IV day 1 cycle 4	84.1		94.2		
Mattiuzzi et al ²³	1) Ondansetron 8 mg IV	n/a	n/a	21 ^a	n/a	Constipation ^c , headache ^c
	2) Palonosetron 0.25 mg IV from day 1 to day 5			31 ^a		
	3) Palonosetron 0.25 mg IV on days 1, 3, and 5			35 ^a		
Dong et al ²⁴	1) Palonosetron 0.25 mg IV	95.4 ^a	90.9 ^a	84.1	79.5	Constipation (15.7%), headache (4.5%), anxiety (2.3%)
	2) Ondansetron 8 mg IV	93.3 ^a	91.9 ^a	60.0	55.5	
Tian et al ²⁵	1) Palonosetron 0.25 mg IV	n/a	66.41 ^a	n/a	53.91 ^a	Leukopenia (12.50%–15.94%), constipation (8.70%–10.16%), fatigue (8.59%–9.42%), alanine or aspartate aminotransferase elevation (6.52%–7.81%), abnormal ECG recordings (5.07%–7.81%), dizziness (7.03%–10.87%), headache (5.80%–6.25%), anemia (4.69%–6.52%), thrombocytopenia (0.78%–6.52%)
	2) Granisetron 3 mg IV		62.32 ^a		52.17 ^a	

Notes: ^aNot statistically significant; ^bthis study was included in the dexamethasone and palonosetron combination section as well; ^cdidn't state proportion of patients experiencing these symptoms.

Abbreviations: CC, complete control; CR, complete response; ECG, electrocardiogram; IV, intravenous; n/a, not available.

Table 5 Study design and characteristics of patient populations in studies administering PALO in combination with other antiemetics

Study	Phase	Intervention	Sample size	Chemotherapy emetogenicity	Mean age, years
DEX					
Ikari et al ¹⁴	n/a	[day 1] 0.75 mg PALO +12–16 mg DEX (unless steroids were previously included) [day 2 onward] 4–8 mg DEX [day 3] 0.75 mg PALO	n=26	HEC or MEC	n/a
Boccia et al ¹⁹	III	Oral PALO:	n=77	MEC	57.1
		1) 0.25 mg	n=78		56.1
		2) 0.50 mg	n=81		55.8
		3) 0.75 mg IV PALO 4) 0.25 mg DEX: 8 mg IV	n=81		57.7
Maemondo et al ²⁶	II	[day 1]:	n=76	HEC	61.7
		1) 0.075 mg	n=77		62.1
		2) 0.25 mg	n=78		62.0
		3) 0.75 mg PALO +12–16 mg DEX [day 2] all groups 8 mg DEX [day 3] all groups 4–8 mg DEX [day 1] 250 µg/5 mL PALO +16 mg DEX [days 2–3] 8 mg DEX every 12 h [days 4–5] 4 mg DEX every 12 h			
Massa et al ²⁷	II	[day 1] all groups: 0.25 mg PALO +8 mg DEX [day 2–3]:	Elderly: n=23 Nonelderly: n=24	HEC or MEC	Elderly: 72.3 Nonelderly: 60.7
Aspro et al ²⁸	n/a	1) Placebo 4 mg DEX bid [day 1] 0.25 mg PALO +8 mg DEX [days 2–3]	n=151 n=149	MEC	52.1 51.2
Celio et al ²⁹	III	1) No additional DEX 8 mg DEX daily	n=166 n=166	MEC	56.9 57.2
		[day 1] 0.25 mg PALO followed by 8 mg DEX [day 1] 0.25 mg PALO +2–8 mg DEX [day 2 onwards] up to 8 mg DEX [day 1 before each cycle] 0.25 mg PALO +20 mg DEX [day 1] 0.75 mg PALO +16 mg DEX before [days 2–3] 8 mg DEX [day 1] 0.25 mg PALO followed by 20 mg DEX	n=68 n=33 n=50 n=538 n=35	MEC n/a n/a HEC HEC	n/a n/a 56.8 57.8 56
Brugnatelli et al ³⁰	n/a	[day 1] 0.25 mg PALO followed by 8 mg DEX	n=68	MEC	n/a
Rozzi et al ³¹	II	[day 1] 0.25 mg PALO +2–8 mg DEX [day 2 onwards] up to 8 mg DEX	n=33	n/a	n/a
Lorusso et al ³²	n/a	[day 1 before each cycle] 0.25 mg PALO +20 mg DEX	n=50	n/a	56.8
Aogi et al ³³	III	[day 1] 0.75 mg PALO +16 mg DEX before [days 2–3] 8 mg DEX	n=538	HEC	57.8
Lorusso et al ³⁴	n/a	[day 1] 0.25 mg PALO followed by 20 mg DEX	n=35	HEC	56
PALO, DEX, and APR					
Gao et al ⁵	n/a	[day 1] APR 125 mg PO; [days 2–3] APR 80 mg PO once daily [days 1–3] PALO 0.5 mg IV once daily [days 1–3] DEX 5 mg IV once daily	n=41	n/a	n/a

Longo et al ³⁷	n/a	[day 1] PALO 0.25 mg IV + DEX 20 mg IV + APR 125 mg PO	n=222	HEC	n/a
		[day 2] APR 80 mg PO + DEX 4 mg PO or IM			
		[day 3] APR 80 mg PO + DEX 4 mg PO or IM			
Grote et al ³⁸	II	[day 1] APR 125 mg + DEX 12 mg PO + PALO 0.25 mg IV	n=58	MEC	n/a
		[days 2–3] APR 80 mg + DEX 8 mg PO qam			
Hesketh and Sanz-Altamira ³⁹	n/a	[day 1] APR 125 mg PO + DEX 8–10 mg IV or PO + PALO 0.25 mg IV	n=36	n/a	n/a
		[days 2–3] DEX 4 mg + APR 80 mg PO qam			
Grunberg et al ⁴⁰	n/a	APR 285 mg PO + DEX 20 mg PO + PALO 0.25 mg IV	n=41	MEC	n/a
Kim et al ⁴¹	n/a	1) PALO 0.25 mg IV	n=115	HEC	54.39
		2) OND, granisetron, dolasetron, or ramosetron			
		all: [day 1] APR 125 mg PO + DEX 12 mg IV; [days 2–3] APR 80 mg + DEX 8 mg PO or IV; [day 4] DEX 8 mg PO or IV			
NEPA (NETU and PALO)					
Aapro et al ⁴²	III	1) NEPA (NETU 300 mg + PALO 0.50 mg) + DEX 12 mg	n=724	MEC	n/a
		2) PALO 0.50 mg + DEX 20 mg day 1	n=725		
Hesketh et al ⁴³	II	1) [day 1] Oral PALO 0.50 mg + oral DEX 20 mg + placebo;	n=136	HEC	n/a
		[days 2–4] Oral DEX 8 mg bid	n=135		
		2) [day 1] Oral NETU 100 mg + oral PALO 0.50 mg + oral DEX 12 mg; [days 2–4] Oral DEX 4 mg bid	n=142		
		3) [day 1] Oral NETU 200 mg + oral PALO 0.50 mg + oral DEX 12 mg; [days 2–4] Oral DEX 4 mg bid	n=143		
		4) [day 1] Oral NETU 300 mg + oral PALO 0.50 mg + oral DEX 12 mg; [days 2–4] Oral DEX 4 mg bid	n=138		
		5) [day 1] Oral APR 125 mg + IV OND 32 mg + oral DEX 12 mg; [days 2–3] Oral APR 80 mg in morning + oral DEX 4 mg bid; [day 4] oral DEX 4 mg bid			

Abbreviations: APR, aprepitant; bid, twice daily; DEX, DEX; HEC, highly emetogenic chemotherapy; h, hours; IM, intramuscular; IV, intravenous; LEC, low emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; n/a, not applicable; NEPA, combination of netupitant and PALO; NETU, netupitant; OND, ondansetron; PO, per oral; PALO, palonosetron; qam, every morning.

Table 6 Efficacy outcomes and adverse events in studies administering PALO in combination with other antiemetics

Study	Intervention	Complete response – acute (%)	Complete control – acute (%)	Complete response – delayed (%)	Complete control – delayed (%)	Adverse events
DEX						
Boccia et al ¹⁹	[day 1] 0.75 mg PALO + 12–16 mg DEX (unless steroids were previously included) [day 2 onward] 4–8 mg DEX [day 3] 0.75 mg PALO	76.9 86.1 85.0 82.9	n/a	57.7 63.3 63.8 68.3	n/a	n/a
Brugnatelli et al ³⁰	Oral PALO: 1) 0.25 mg 2) 0.50 mg 3) 0.75 mg IV PALO 4) 0.25 mg DEX: 8 mg IV [day 1]: 1) 0.075 mg 2) 0.25 mg 3) 0.75 mg PALO + 12–16 mg DEX [day 2] all groups 8 mg DEX [day 3] all groups 4–8 mg DEX [day 1] 250 µg/5 mL PALO + 16 mg DEX	75.0	73.5	75.0	72.1	Constipation (14.7%), insomnia (10.3%), abdominal pain (5.8%)
Rozzi et al ³¹	DEX: 8 mg IV [day 1]: 1) 0.075 mg 2) 0.25 mg 3) 0.75 mg PALO + 12–16 mg DEX [day 2] all groups 8 mg DEX [day 3] all groups 4–8 mg DEX [day 1] 250 µg/5 mL PALO + 16 mg DEX	n/a	91.0	n/a	88.0	Headache (21%), constipation (15%), abdominal pain (3%)
Lorusso et al ³²	[day 1] 250 µg/5 mL PALO + 16 mg DEX [days 2–3] 8 mg DEX every 12 h [days 4–5] 4 mg DEX every 12 h [day 1] all groups: 0.25 mg PALO + 8 mg DEX [day 2–3]: 1) Placebo 4 mg DEX bid [day 1] 0.25 mg PALO + 8 mg DEX [days 2–3] 1) No additional DEX 8 mg DEX daily [day 1] 0.25 mg PALO followed by 8 mg DEX	n/a	n/a	76.0–88.0	62.0–88.0	Not specified
Aogi et al ³³	[day 1] all groups: 0.25 mg PALO + 8 mg DEX [day 2–3]: 1) Placebo 4 mg DEX bid [day 1] 0.25 mg PALO + 8 mg DEX [days 2–3] 1) No additional DEX 8 mg DEX daily [day 1] 0.25 mg PALO followed by 8 mg DEX	72.0–77.0	54.8–61.0	56.0–63.0	34.8–40.9	Constipation (0.6%–17.3%)
Ikari et al ¹⁴	[day 1] 0.25 mg PALO + 8 mg DEX [days 2–3] 1) No additional DEX 8 mg DEX daily [day 1] 0.25 mg PALO followed by 8 mg DEX	96.2	92.3	76.9	61.5	Constipation (77%), diarrhea (15.4%), pain (7.7%), fever (7.7%)
Maemondo et al ²⁶	[day 1] 0.25 mg PALO followed by 8 mg DEX	77.6 ^a 81.8 ^a 79.5 ^a	Only stated that it was similar to complete response rate	40.8 53.2 56.4	Only stated that it was similar to complete response rates	Constipation (6.6%–14.1%), headache (2.6%–6.5%), hiccups (0%–2.6%), rash (1.3%–2.6%), cold sweat (0%–2.6%), angiodema (0%–2.6%) Constipation, ^a anxiety ^b
Massa et al ²⁷	[day 1] 0.25 mg PALO + 2–8 mg DEX [day 2 onwards] up to 8 mg DEX [day 1 before each cycle] 0.25 mg PALO + 20 mg DEX	Elderly: 74.0 ^a Nonelderly: 78.0 ^a 85.7	Elderly: 74.0 ^a Nonelderly: 78.0 ^a 82.9	Elderly: 78.0 ^a Nonelderly: 83.0 ^a 82.9	Elderly: 78.0 ^a Nonelderly: 83.0 ^a 77.1	Constipation (11.0%), headache (8.6%)
Lorusso et al ³⁴	[day 1] 0.25 mg PALO + 2–8 mg DEX [day 2 onwards] up to 8 mg DEX [day 1 before each cycle] 0.25 mg PALO + 20 mg DEX	Elderly: 74.0 ^a Nonelderly: 78.0 ^a 85.7	Elderly: 74.0 ^a Nonelderly: 78.0 ^a 82.9	Elderly: 78.0 ^a Nonelderly: 83.0 ^a 82.9	Elderly: 78.0 ^a Nonelderly: 83.0 ^a 77.1	Constipation (11.0%), headache (8.6%)

Aapro et al ²⁸	[day 1] 0.75 mg PALO + 16 mg DEX before	69.5 68.5	47.0 49.7	62.3 65.8	50.3–71.5 55.0–63.8	Headache (15.9%–18.8%), constipation (2.6%–7.4%), erythema (5.3%–5.4%)
Celio et al ²⁹	[day 1] 0.25 mg PALO followed by 20 mg DEX	88.6 84.3	87.1 82.0	68.7 77.7	66.3 75.8	Headache (13.9%–19.9%), constipation (9.6%–10.8%), fatigue (4.2%–9.0%)
Palonosetron, DEX, and APR						
Longo et al ³⁷	[day 1] APR 125 mg PO; [days 2–3] APR 80 mg PO once daily [days 1–3] PALO 0.5 mg IV once daily	97.7	n/a	72.5	n/a	Constipation (39%), headache (5%)
Grote et al ³⁸	[days 1–3] DEX 5 mg IV once daily [day 1] PALO 0.25 mg IV + DEX 20 mg IV + APR 125 mg PO [day 2] APR 80 mg PO + DEX 4 mg PO or IM [day 3] APR 80 mg PO + DEX 4 mg PO or IM	88	n/a	78	n/a	Constipation (21%), diarrhea (17%), fatigue (16%), insomnia (14%), thrombocytopenia (10%)
Gao et al ⁵	[day 1] APR 125 mg + DEX 12 mg PO + PALO 0.25 mg IV [days 2–3] APR 80 mg + DEX 8 mg PO qam	63.4	n/a	78.0	n/a	Hiccups (31.7%), fatigue (17.1%), headache (14.6%), constipation (12.2%)
Hesketh and Sanz-Altimira ³⁹	[day 1] APR 125 mg PO + DEX 8–10 mg IV or PO + PALO 0.25 mg IV [days 2–3] DEX 4 mg + APR 80 mg PO qam	81	53	61	36	Headache (15%), fatigue (10%)
Grunberg et al ⁴⁰	APR 285 mg PO + DEX 20 mg PO + PALO 0.25 mg IV	76	n/a	66	n/a	Headache (78.0%), fatigue (75.6%), anorexia (48.8%), insomnia (36.6%), constipation (34.1%), hot flash (22.0%), diarrhea (22.0%), bone pain (14.6%), dyspnea (14.6%), ALT elevation (14.6%), dyspepsia (14.6%)
Kim et al ⁴¹	1) Palonosetron 0.25 mg IV 2) OND, granisetron, dolasetron, or ramosetron all: [day 1] APR 125 mg PO + DEX 12 mg IV; [days 2–3] APR 80 mg + DEX 8 mg PO or IV; [day 4] DEX 8 mg PO or IV	89.0 ^a 88.1 ^a	87.7 ^a 85.7 ^a	54.8 ^a 54.8 ^a	52.0 ^a 54.8 ^a	Not specified

(Continued)

Table 6 (Continued)

Study	Intervention	Complete response – acute (%)	Complete response – acute (%)	Complete control – delayed (%)	Adverse events
NEPA (NETU and PALO)					
Aapro et al ⁴²	1) NEPA (NETU 300 mg + PALO 0.50 mg) + DEX 12 mg	88.4	n/a	n/a	Headache (3.2%), constipation (2.1%)
	2) PALO 0.50 mg + DEX 20 mg	85.0			
Hesketh et al ⁴³	day 1				
	1) [day 1] Oral PALO 0.50 mg + oral DEX 20 mg + placebo; [days 2–4] Oral DEX 8 mg bid	89.7 ^a	n/a	n/a	Hiccups (0%–5.1%), headache (0.7%–2.2%)
	2) [day 1] Oral NETU 100 mg + oral PALO 0.50 mg + oral DEX 12 mg; [days 2–4] Oral DEX 4 mg bid	93.3 ^a			
		92.7 ^a			
	3) [day 1] Oral NETU 200 mg + oral PALO 0.50 mg + oral DEX 12 mg; [days 2–4] Oral DEX 4 mg bid	98.5			
	4) [day 1] Oral NETU 300 mg + oral PALO 0.50 mg + oral DEX 12 mg; [days 2–4] Oral DEX 4 mg bid	94.8 ^a			
	5) [day 1] Oral APR 125 mg + IV OND 32 mg + oral DEX 12 mg; [days 2–3] Oral APR 80 mg in morning + oral DEX 4 mg bid; [day 4] oral DEX 4 mg bid				

Notes: ^aNot statistically significant; ^ba cumulated proportion of patients experiencing adverse events was not given.

Abbreviations: ALT, alanine transaminase; APR, aprepitant; bid, twice daily; DEX, dexamethasone; h, hours; IM, intramuscular; IV, intravenous; n/a, not applicable; NEPA, combination of netupitant and PALO; NETU, netupitant; OND, ondansetron; PO, per oral; PALO, palonosetron; qam, every morning.

higher dose test group, whereas only 26% of patients in the low dose test group achieved CR. The authors also noted that the lower dose group exhibited decreased CC compared to the higher dose groups. They concluded that differences between the test groups reached significance at the 30 µg/kg point.¹⁵

Phase II studies of palonosetron-only therapy

A number of Phase II studies have examined the use of palonosetron alone for CINV prevention (Tables 3 and 4). Within each study, the use of other antiemetics was prohibited. In an open label, single arm investigation of palonosetron with 34 patients receiving low emetogenic chemotherapy (LEC), 88.2% and 67.6% of patients experienced CR during the acute and delayed phases, respectively. CC was similar at 85.3% and 64.7% for acute and delayed phases. This group suggested that palonosetron was effective in preventing CINV for patients receiving LEC.¹⁸

Another study evaluated the efficacy of palonosetron in 74 patients with aggressive non-Hodgkin's lymphoma who were receiving MEC. Patients received a single dose of 0.25 mg of palonosetron IV. During the acute phase, 90.7% of patients reported a CR while 88.4% of patients reported a CR during the delayed phase. CC was observed in 89.5% of patients during the acute phase and 84.9% during the delayed phase. This study demonstrated the effectiveness and potential role of palonosetron in patients with non-Hodgkin's lymphoma receiving MEC.⁹

Phase III studies of palonosetron-only therapy

Several Phase III clinical trials have examined the safety and efficacy of palonosetron in preventing CINV (Tables 3 and 4). One study compared different doses of oral palonosetron with IV palonosetron in 635 patients receiving MEC (Table 3).¹⁹ The proportion of CRs observed in the acute phase was higher for all doses administered orally (62.8%–70.1% orally versus 57.5% IV), with the highest resulting from the 0.25 mg dose (70.1%). In the delayed phase however, a greater proportion of CR was observed in patients who received IV palonosetron. Overall, it was found that the oral doses were similar in efficacy when compared to the IV formulation. However, this group also went on to recommend oral palonosetron 0.50 mg as a therapeutic option, citing its numeric superiority in efficacy.¹⁹

In another study, the efficacy and safety of palonosetron was evaluated and compared to dolasetron in 569 subjects. The subjects were randomized to receive either IV palonosetron or dolasetron. The primary hypothesis was that at least

one dose of palonosetron was noninferior to dolasetron. This hypothesis was supported during the acute phase as the CR rates were 63.0%, 57.1%, and 52.9% of patients for 0.25 mg palonosetron, 0.75 mg palonosetron, and 100 mg dolasetron, respectively. Furthermore, CR rates observed during the delayed phase were significantly higher for both doses of palonosetron compared to dolasetron. This group concluded that a single dose of palonosetron is more effective than a single dose of dolasetron in both acute and delayed CINV prophylaxis in patients receiving MEC.²⁰

Gralla et al²¹ on the other hand, compared palonosetron with ondansetron. A total of 563 subjects were randomized to receive intravenously, either palonosetron or ondansetron. The CR rates observed in patients who received 0.25 mg of palonosetron were significantly different than those who received ondansetron during the acute (81.0% vs 68.6%) and delayed phases (74.1% vs 55.1%). However, 0.75 mg of palonosetron did not yield any significantly different CR rates in both acute and delayed phases. CC rates for 0.25 mg and 0.75 mg were both significantly higher than ondansetron during the delayed phase. The study group suggested that 0.25 mg of palonosetron was more effective than 32 mg ondansetron in preventing acute and delayed CINV.

Phase IV studies of palonosetron-only therapy

The efficacy of palonosetron in patients with non-Hodgkin's lymphoma undergoing MEC was assessed in a Phase IV open-labeled, uncontrolled study. Patients received 0.25 mg of palonosetron on day 1 of cycle 1, and at each subsequent cycle. For all cycles, the initial CR rate observed during the acute phase increased as patients entered into the delayed phase. Within the delayed phase, the CR increased from 83.0% to 93.9% from cycle 1 to 2 and remained approximately the same in subsequent cycles. Overall, palonosetron showed control of CINV in both the acute and delayed phases in this patient group.²²

Other studies

Mattiuzzi et al²³ conducted a comparative randomized controlled trial in 143 patients with acute myelogenous leukemia receiving HEC. Subjects were allotted to receive either ondansetron 8 mg, 0.25 mg IV palonosetron from day 1 to day 5, or palonosetron 0.25 mg IV on days 1, 3, and 5. The CR during the delayed phase were reported to be 21% and 31% for the ondansetron and palonosetron study groups on days 1 to 5, respectively. Palonosetron study groups on days 1, 3, and 5 reported CR rates of 35% in the delayed

phase. However, the CR rates were not significantly different across all study arms.

Dong et al²⁴ compared palonosetron to ondansetron in 89 subjects with non-small-cell lung carcinoma (NSCLC) receiving HEC. This group found that the proportion of CR and CC observed during the acute phase were not significantly different between palonosetron and ondansetron groups. Interestingly, the proportions observed during the delayed phases were significantly higher in the palonosetron group with a CR rate of 84.1% and CC rate of 79.5%, compared to 60.0% and 55.5%, respectively in the ondansetron group. This study suggested that palonosetron is more effective in preventing delayed nausea and vomiting than is ondansetron in patients with NSCLC.

Another study compared palonosetron with granisetron in 122 patients.²⁵ The subjects in this study received either HEC or MEC and were randomized to receive either palonosetron intravenously in the first cycle and granisetron intravenously in the second cycle or vice versa. The CR rates of palonosetron for acute and delayed phases were not statistically different than that of granisetron, but were higher than granisetron nonetheless. The CR for palonosetron was 71.09% in the acute phase as opposed to 60.16% in the delayed phase. Overall, palonosetron was effective and noninferior to granisetron in preventing CINV in both acute and delayed phases.

Safety and tolerability of palonosetron-only therapy

The most common adverse events reported by patients among the included studies can be found in Table 4. Palonosetron has been shown to be safe and tolerable as an antiemetic drug. The majority of patients who experienced adverse events reported them as mild or moderate, whereas severe symptoms were determined to be unrelated to the study medication. The most common symptoms across palonosetron-only therapy included studies were: constipation, headache, fatigue, and dizziness.^{9,15,18–25}

Combination studies – dexamethasone

Dexamethasone is a corticosteroid that when administered with 5-HT₃RAs increases the antiemetic effect. One explanation of dexamethasone's mechanism of action is that it increases the low cortisol level that is associated with nausea and vomiting.

Boccia et al¹⁹ randomized patients to receive either oral or IV formulations of palonosetron, with or without dexamethasone. This group found that additional dexamethasone

was associated with higher CR rates during the acute phase. In oral formulations, the 0.75 mg strength presented with the greatest difference in CR rates: 85.0% with concomitant dexamethasone, compared to 62.8% without. The difference was also substantial in the IV formulation (0.25 mg): 82.9% with concomitant dexamethasone; 57.5% without. There was also a greater CR rate in patients that were administered dexamethasone during the delayed phase, but the difference was much less pronounced. Interestingly, the oral 0.25 mg strength revealed CR rates that were lower with concomitant dexamethasone. This led the group to recommend 0.50 mg of palonosetron as the starting therapeutic option, should dexamethasone also be included in the drug regimen.

In a study by Maemondo et al²⁶ 231 subjects were randomized to receive either 0.075, 0.25, or 0.75 mg of palonosetron along with a dose of dexamethasone (12–16 mg) on day 1, followed by dexamethasone doses over the subsequent 2 days. Groups were similar in baseline characteristics, and all individuals were receiving HEC. Across all groups, more than 75% of patients reported CR in the acute phase. Within the delayed phase, only the 0.25 mg and 0.75 mg groups noted that greater than 50% of patients had a CR. CC rates were similar to the CR rates in their respective phases.

A number of trials have demonstrated the utility of combining palonosetron and dexamethasone in specific patient cohorts, including breast and colorectal cancers, as well as glioblastoma; however, the results of these trials were not compared to single agent palonosetron (Tables 5 and 6).^{16,19,26–34}

Massa et al²⁷ examined palonosetron and dexamethasone in elderly and nonelderly individuals receiving either MEC or HEC. Across all groups, more than 75% of patients reported a CR in both the acute and delayed phases. Nonelderly patients reported higher percentages of CR in both phases. Additionally, this study found an increase in the percentage of CR from the acute to the delayed phases for both groups: a 4% increase in elderly individuals, and 5% in nonelderly individuals.

The efficacy of the dexamethasone–palonosetron combination, administered exclusively on day 1 as opposed to subsequent doses of dexamethasone, has also been examined.^{28,29} Both Aapro et al²⁸ and Celio et al²⁹ conducted their studies using 0.25 mg palonosetron with up to 8 mg of dexamethasone in patients receiving MEC. Patients received either 8 mg of dexamethasone or no dexamethasone, on days 2 and 3. In the acute phase, both studies reported a higher percentage of CR in patients, although the difference was not statistically significant. Both groups also found increased CR rates in

the delayed phase. In terms of CC, Celio et al²⁹ uncovered a similar trend (ie, greater percentage of those achieving CC in those without subsequent doses of dexamethasone in the acute phase, followed by a greater percentage in those who received additional doses in the delayed phase), whereas the opposite trend was discovered in the study by Aapro et al.²⁸

Safety

Palonosetron, like other members of the 5-HT₃RAs, has the potential to affect electrocardiographic parameters, in particular prolongation of the QT interval, which has been associated with life threatening arrhythmias and death.^{4,35,36} One meta-analysis suggested that palonosetron was safer than first generation 5-HT₃RAs with respect to the change in QT interval.⁴ Additionally, Yavas et al³⁵ and Dogan et al³⁶ have also conducted prospective studies to determine the effect of antiemetic prophylaxis on QT interval. In both studies, patients were administered 8 mg of dexamethasone and 0.25 mg of palonosetron intravenously. Although changes in QT interval were found by both studies, neither groups found their results to be statistically significant. In both cases then, it was thus concluded that palonosetron has no acute arrhythmogenic potential.^{35,36}

The most common side effects among these studies were headache and constipation, both of which were reported as mild to moderate in intensity. Treatments were well tolerated overall, as severe side effects experienced by test subjects were deemed unrelated to the dexamethasone and palonosetron regimen.^{29,31,34}

Combination studies – palonosetron, dexamethasone, and aprepitant

Studies have also been conducted to determine the efficacy of the combination of palonosetron, dexamethasone, and aprepitant in patients receiving HEC (Tables 5 and 6).^{5,37–41} Three studies examined the combination in patients receiving cisplatin-based chemotherapy, each lasting 3 days.^{5,37,38} Each study utilized a single oral dose of aprepitant 125 mg on day 1, followed by single oral doses of aprepitant 80 mg on days 2 and 3. Longo et al³⁷ and Grote et al³⁸ both administered palonosetron as a single IV dose of 0.25 mg before chemotherapy to 222 patients and 58 patients, respectively. Palonosetron was not given to patients during the remaining 2 days in either study. Gao et al⁵ on the other hand, administered palonosetron over the entire 3-day period as IV doses of 0.5 mg once daily to 41 patients. Dexamethasone was also administered differently between each study. Gao et al⁵ revealed the lowest percentage of patients with CRs in both

the acute and delayed stages (63.4% and 78.0% respectively), but noted that the efficacy of the study is maintained over multiple cycles. Longo et al³⁷ had the largest sample size of the three studies (n=222), and also reported the highest percentages in completed responses over the acute phase (97.7%). Despite slight differences in regimen, each study found the combination of medications to be effective and well tolerated. Constipation, headache, and fatigue were the most commonly reported side effects. However, Grote et al³⁸ reported that the majority of side effects experienced were mild in nature.

The triple therapy was also studied in patients receiving doxorubicin and cyclophosphamide (AC).^{39,40} Hesketh and Sanz-Altamira³⁹ administered aprepitant 125 mg, dexamethasone 8–10 mg and palonosetron 0.25 mg on day 1, followed by dexamethasone 4 mg and aprepitant 80 mg once daily for days 2–3 to 36 patients. Grunberg et al⁴⁰ on the other hand, opted to administer aprepitant 286 mg, dexamethasone 20 mg, and palonosetron 0.25 mg on day 1 only to 41 patients. Both studies found the treatment to be well tolerated overall, with the majority of side effects to be minor in nature. Despite having a similar regimen to the studies involving cisplatin-based chemotherapy, Hesketh and Sanz-Altamira³⁹ found that further improvement in efficacy is warranted, as a only half of the study patients were able to achieve CR overall.³⁹ On the other hand, single-day triple-therapy may be effective against MEC, and requires more study.⁴⁰

Despite the vast research that has been conducted using the triple therapy, one group concluded that this combination with palonosetron as the 5-HT₃RA did not significantly improve CINV compared to those containing another 5-HT₃RA in patients receiving multiday HEC.⁴¹ The CR and CC rates in both study arms were similar with 89.0% and 87.7%, respectively in palonosetron-based triple therapy.

Combination studies – netupitant and palonosetron (NEPA)

A few studies have been conducted to evaluate the efficacy of a new NK-1 RA called netupitant that works in combination with palonosetron to improve control of CINV. The antiemetic effect is due to the ability of palonosetron to inhibit crosstalk between 5-HT₃ and NK-1 receptors as well as both palonosetron and netupitant working to inhibit SP.⁴² The characteristics of these studies have been summarized in Tables 5 and 6. A Phase II study was conducted to determine an appropriate clinical dose of NEPA to evaluate in subsequent Phase III trials.⁴³ Subjects were randomized to “PALO”, “NEPA₁₀₀”, “NEPA₂₀₀”, “NEPA₃₀₀”, or “APR + OND” arms. The 136 patients in the PALO (palonosetron) arm

received of 0.50 mg oral palonosetron, 20 mg oral dexamethasone, and placebo, followed by 8 mg of oral dexamethasone for days 2–4. There were 135, 136, 142, and 143 patients in each NEPA arm that received 100, 200, or 300 mg of netupitant rather than placebo, respectively. For the APR (aprepitant) + OND (ondansetron) arm, 125 mg oral aprepitant, 32 mg IV ondansetron, and 12 mg oral dexamethasone were given to subjects on day 1 followed by 80 mg oral aprepitant and 4 mg oral dexamethasone on days 2–4. Compared to the PALO arm, this group found that each NEPA dose increased the prevention of both acute and delayed CINV following HEC (Table 6). The CR of the PALO arm was 89.7% in the acute phase whereas the NEPA arms ranged from 92.7% to 98.5%. In the delayed phase, the CR of the PALO arm was 80.1% and the NEPA arms ranged from 90.4% to 91.2%. This group suggested NEPA₃₀₀ was an appropriate dose due to the higher CR rate of 98.5% in the acute phase and 90.4% in the delayed phase, as observed in their patient group.⁴³

A subsequent Phase III study compared the safety and efficacy of the additional 300 mg netupitant to palonosetron.⁴² Aapro et al⁴² randomized patients being treated with MEC to receive either NEPA plus dexamethasone (n=724) or palonosetron plus dexamethasone (n=725). The researchers showed that NEPA plus a single dose of dexamethasone was significantly better than the combination of palonosetron and dexamethasone in preventing CINV in both the acute and delayed phases. Adding dexamethasone to NEPA increased the CR rate from 85.0% to 88.4% in the acute setting and from 69.5% to 76.9% in the delayed setting.⁴²

In both studies, the most common reported adverse event was headache (3.2%, and 0.7%–2.2%, respectively). Additionally, constipation and hiccups were also noted to be common adverse events (5.1% occurrence). The majority of these events were considered to be mild or moderate in nature.^{42,43}

Patient satisfaction and quality of life

Only a few studies discussed patient satisfaction with antiemetic therapy^{9,30} and the impact of treatment on quality of life.^{9,28,30,37} Global satisfaction was rated based on a visual analog scale from 0 (completely unsatisfied) to 10 (completely satisfied).^{9,30} Di Renzo et al⁹ found that patients receiving single dose palonosetron had a median global satisfaction score of 8.0 (based on a visual analog scale from 1 to 10) with the antiemetic therapy. With the administration of dexamethasone, the median patient reported global satisfaction score was 9.0.³⁰

Longo et al³⁷ found that fatigue and pain were the major factors that affected quality of life. In addition, 33%

of patients felt a reduction in their social activity during antiemetic therapy.³⁷ However, a study conducted by Aapro et al²⁸ found that, overall, the quality of life was preserved. Evaluated with the functional living index-emesis (FLIE) questionnaire for nausea and vomiting, it was found that no statistically significant differences in quality of life were observed with respect to therapy.²⁸

Discussion

Nausea and vomiting is a common side effect of chemotherapy that can be difficult to prevent and subsequently control. The reason for this is likely multifactorial in nature, but may be due to the lack of complete understanding surrounding the mechanism of CINV, in addition to interpatient differences in toxicity to chemotherapy agents.¹

Many studies have been conducted in order to prevent the occurrence of CINV. Historically, dopamine receptors have been the targets of interest; however, since the discovery of 5-HT₃ receptor involvement in the pathophysiology of CINV, a near paradigm shift has occurred in how this chemotherapy-induced toxicity is managed.

Palonosetron, a second generation 5-HT₃RA, has a strong binding affinity to the 5-HT₃ receptor and has been shown to be an effective treatment for both acute and delayed phase CINV.⁹ In addition to its ability to bind tightly to serotonin receptors, palonosetron partitions into tissue to a high extent and as a result demonstrates a relatively long half-life of approximately 40 hours, which may contribute to its effect in the delayed phase of CINV.^{10,12–16}

Many studies have found evidence supporting the potential role of palonosetron in CINV treatment. A Phase II study concerning palonosetron as a treatment with 34 patients given LEC found it to be an effective alternative, citing the fact that more than 50% of patients taking part achieved CC.¹⁸ A number of studies have also examined its use in patients receiving MEC. Di Renzo et al⁹ in particular found very promising results in terms of its effectiveness, as more than 75% of 86 patients were able to achieve CC in both acute and delayed phases. Treatment has also been conducted in 44 patients receiving HEC, where significantly higher rates of CR and CC have been found for palonosetron in the delayed phase.²⁴ Overall, palonosetron alone has been shown to be effective in emetogenic chemotherapy, particularly in the delayed phase. With respect to treatment following HEC, however, some studies have not been successfully reproduced, warranting further examination.²³

Formulations of palonosetron include oral and IV routes. Boccia et al¹⁹ found that while oral administration provided greater results in the acute phase, an IV injection was more

effective in the delayed phase, at comparable doses. In comparison to existing treatments; studies have suggested that palonosetron is superior or noninferior compared with first generation 5-HT₃ RAs, such as dolasetron and ondansetron, when administered at much lower doses.^{20,21}

Several studies have also combined the palonosetron regimen with other. With the addition of dexamethasone, Boccia et al²⁰ found greater CR rates in the acute and delayed phases, with the increase in the acute phase being more pronounced. Evidence also favors the combination's effect in response to many forms of chemotherapy.^{26–34}

Various studies have attempted to further increase the efficacy of the palonosetron–dexamethasone combination by adding yet another antiemetic known as aprepitant. Aprepitant is an NK-1 RA, and its addition was tested in patients receiving HEC. Although dosing regimens differed, the triple-therapy was found to be very well tolerated.^{37–39} Some studies however, have found contrary evidence, citing disparities in efficacy.⁴⁰ In MEC cohorts, Grunberg et al⁴⁰ found that single-day triple-therapy may be effective in treating CINV. This represents yet another step toward realizing the full potential of this combination, and future studies should seek to establish its place in therapy as well. Overall, more research is required in order to establish the triple therapy's place in CINV treatment. However, current results stand as a testament as to the steps that have been taken toward CINV treatment, particularly in individuals receiving HEC.

The combination of NEPA has also been examined. This combination has been reported to be very well tolerated, and it was found that CINV prevention increased with larger doses of netupitant. It is dosed at 300 mg once daily and has been shown to be very successful in the prevention of CINV following HEC and MEC.^{35,36}

Overall, a major drawback of first generation 5-HT₃ RAs includes prolongation of the QT interval. Studies have shown alterations in the QT interval while on palonosetron are not statistically significant, making it less concerning for use in patients suffering from cardiac diseases.⁴² While some severe adverse reactions have been reported, study coordinators have dubbed them as unrelated to the treatment regimen. Overall, side effects as a result of palonosetron administration, alone and in combination with other antiemetics, have all been mild to moderate in nature, with headache, constipation, and fatigue being the most common.

Overall, palonosetron stands as an effective option for CINV treatment. It is very well tolerated, and its use is advantageous over first generation serotonin receptor antagonists. Several studies have examined its relative efficacy and have deemed it superior to current antiemetic CINV treatments,

as it is able to prevent both acute and delayed phase emesis. Future research should identify the most promising antiemetic combinations, especially for patients receiving HEC.

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Disclosure

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