Support Care Cancer (2013) 21:1453–1460
DOI 10.1007/s00520-012-1691-5

ORIGINAL ARTICLE

Efficacy of oral palonosetron compared to intravenous palonosetron for the prevention of chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy: a phase 3 trial

Ralph Boccia · Steven Grunberg · Edwin Franco-Gonzales · Edward Rubenstein · Daniel Voisin

Received: 26 July 2012 / Accepted: 10 December 2012 / Published online: 26 January 2013

Abstract
Background Palonosetron (Aloxi®, Onicit®) is a pharmacologically unique 5-HT_3 receptor antagonist (RA) approved as a single IV injection for the prevention of nausea and vomiting induced by chemotherapy (CINV) of either moderate or highly emetogenic potential (MEC and HEC, respectively). An oral palonosetron formulation has been developed and compared to the IV formulation.

Methods In this multinational, multicenter, double-blind, double-dummy, dose-ranging trial, 651 patients were randomly assigned to receive one of the following as a single dose prior to moderately emetogenic chemotherapy: oral palonosetron 0.25, 0.50, and 0.75 mg or IV palonosetron 0.25 mg. Patients were also randomized (1:1) to receive dexamethasone 8 mg IV or matched placebo on day 1. The primary endpoint was complete response (CR; no emesis, no rescue therapy) during the acute phase (0–24 h).

Results Acute CR rates were 73.5, 76.3, 74.1, and 70.4 % for all patients receiving the palonosetron 0.25, 0.50, and 0.75 mg oral doses, and for IV palonosetron 0.25 mg, respectively; delayed CR (24–120 h) rates were 59.4, 62.5, 60.1, and 65.4 %, and overall CR (0–120 h) rates were 53.5, 58.8, 53.2, and 59.3 %, respectively. The addition of dexamethasone improved emetic control (acute CR rate) by at least 15 % for all groups except oral palonosetron 0.25 mg, where the acute CR improvement was approximately 7 %. Adverse events were similar in nature, incidence, and intensity for all oral and IV palonosetron groups, and were the expected adverse events for 5-HT_3 RAs (primarily headache and constipation).

Conclusion Oral palonosetron has a similar efficacy and safety profile as IV palonosetron 0.25 mg and may be the preferred formulation in certain clinical situations. Among the tested oral treatments, a palonosetron 0.50-mg oral dose has been favored for the prevention of CINV in patients receiving moderately emetogenic chemotherapy due to a numerical gain in efficacy without a side effect disadvantage.

R. Boccia
Center for Cancer and Blood Disorders,
6420 Rockledge Drive, Suite 4100,
Bethesda, MD 20817,, USA
e-mail: rboccia@ccbdmd.com

S. Grunberg
Division of Hematology/Oncology,
89 Beaumont Avenue-Given E214,
Burlington, VT 05405,, USA
e-mail: Steven.Grunberg@vtmednet.org

E. Franco-Gonzales
Clinica de Merida, Ave Itzaes No. 242 Int.
129 Piso 1 x 25 y 27 Colonia Garcia Gineres,
97070, Merida, Yucatan, Mexico
e-mail: dr.edwinfranco@hotmail.com

E. Rubenstein
2154 Dryden Road,
Houston, TX 77030, USA
e-mail: erubenstein@informgenomics.com

D. Voisin (✉)
Helsinn Healthcare SA, via Pian Scairolo 9,
6912 Lugano, Switzerland
e-mail: dvo@helsinn.com

Keywords Palonosetron · Chemotherapy-induced nausea and vomiting · Moderately emetogenic chemotherapy · 5-Ht_3 receptor antagonist

Introduction

Chemotherapy is frequently associated with nausea and vomiting that can severely impair the ability of patients with cancer to maintain daily functioning [1]. Since their introduction into routine clinical practice, 5-HT_3 receptor antagonists (RAs) have become the cornerstone of current antiemetic prophylaxis and are an integral part of preventive strategies for chemotherapy-induced nausea and vomiting (CINV) [2]. The currently approved 5-HT3RAs include ondansetron, granisetron, tropisetron, dolasetron, palonosetron, ramosetron, and azasetron.

Palonosetron is a pharmacologically unique 5-HT3RA approved by the US Food and Drug Administration and European Medicines Agency for the prevention of nausea and vomiting associated with moderately and highly emetogenic chemotherapy (CINV) as a single intravenous dose given before chemotherapy. Palonosetron can provide protection from emesis and nausea during both the acute and the delayed phases of CINV [3–5]. It has a chemical structure that does not resemble the older 5-HT3RAs and exhibits distinct binding properties and a unique interaction with the 5-HT3 receptor [6]. Although a similar pharmacokinetic profile is achieved with similar oral and intravenous doses of palonosetron in terms of area-under-the-curve drug exposure (unpublished data), the possibility that the lower peak concentration following oral administration might adversely affect efficacy during the acute period suggested that higher oral doses should be evaluated.

Dexamethasone is a standard component of antiemetic combination regimens with first-generation 5HT3 RAs. The present study investigated the efficacy and safety of a single oral dose of palonosetron (0.25, 0.50, and 0.75 mg) compared to a single IV dose of palonosetron (0.25 mg) in the prevention of acute and delayed CINV in patients receiving moderately emetogenic chemotherapy and also explored the contribution of dexamethasone at these different dose levels.

Methods

Study characteristics

This was a randomized, multinational, multicenter, double-blind, double-dummy, dose-ranging trial in which patients were randomly assigned (stratified by gender and history of chemotherapy [naïve vs non-naïve]) to one of four treatments: oral palonosetron (0.25, 0.50, or 0.75 mg) or IV palonosetron (0.25 mg). The study was approved by an appropriate Institutional Review Board and Ethical Committee at each participating site. The study was conducted in 46 centers, 24 in Europe, 7 in Mexico, and 15 in the USA. Patients in each treatment group were randomized (1:1 ratio) to receive either a single dose of dexamethasone (8 mg IV) or matched placebo on day 1 in addition to palonosetron.

Main inclusion and exclusion criteria

Eligible patients were male or female, 18 years of age or older, with histologically or cytologically confirmed malignant disease, Karnofsky index ≥50 %, either naïve or non-naïve to cancer chemotherapy, and scheduled to receive a single IV dose of at least one of the following MEC agents administered on day 1: any dose of oxaliplatin, carboplatin, epirubicin, idarubicin, doxorubicin, ifosfamide, irinotecan, daunorubicin, or cyclophosphamide <1,500 mg/m^2 or cytarabine >1 g/m^2. Patients were excluded if treated with commercially available IV palonosetron 0.25 mg within 2 weeks prior to the start of study treatment or if scheduled to receive any oral or intravenous dose of highly emetogenic chemotherapy, radiotherapy of the upper abdomen or cranium, or total body irradiation on days 1 to 5. Patients were excluded if receiving any low-level emetogenic chemotherapeutic agent (i.e., docetaxel, paclitaxel, or pemetrexed) during days 1 to 5 if, in the investigator's opinion, this necessitated co-administration of antiemetics.

If a patient had known hepatic, renal, or cardiovascular impairment or had a known history or predisposition to cardiac conduction interval abnormalities, including prolonged QTc, and was scheduled to receive the above-mentioned chemotherapeutic agents, he/she could be enrolled in the study at the discretion of the investigator. Reliable contraceptive measures and a negative pregnancy test at the pretreatment (screening) visit were required for female patients of childbearing potential.

Evaluation of efficacy and safety

The primary efficacy endpoint was complete response (CR: no emesis, no rescue antiemetics) during the acute phase (0–24 h after the start of the administration of the first [most] emetogenic chemotherapeutic agent). The key secondary endpoint was CR rates during the delayed (24–120 h) phase. Additional secondary endpoints were the overall CR rates (0–120 h) after administration of chemotherapy, the proportion of patients with complete control (defined as CR and no more than mild nausea), without emetic episodes, without nausea, and without

rescue medication, as well as the severity of nausea (four-point Likert scale: none, mild, moderate, severe), the time to first emetic episode, and patient global satisfaction with antiemetic therapy. These parameters were assessed and reported at various intervals during 0–120 h, as acute, delayed, and overall phases. Safety was assessed based on occurrence of adverse events, vital signs, physical examination, 12-lead ECG, and laboratory parameters. For all ECGs, PR, QRS, QT, QTcB, and QTcF intervals, and heart rate were analyzed.

Statistical methods

The primary efficacy hypothesis was that at least one dose of oral palonosetron was non-inferior to the approved IV dose of palonosetron (0.25 mg) using a maximum delta of 15 %, considering the CR rate at 24 h. To demonstrate non-inferiority, the lower bound of the two-sided 98.3 % confidence interval of the difference between the 0–24 h CR rates for each oral and IV dose of palonosetron were compared to the preset threshold (−15 % difference). Results were evaluated on the full analysis set (FAS), defined as all randomized patients who received the study medication and at least moderately emetogenic chemotherapy. The CR rates during the other time periods (including the delayed and overall phases) were examined using the same statistical methods as for the primary efficacy endpoint (two-sided 98.3 % confidence intervals).

The differences between the three oral doses of palonosetron were tested using a two-sided non-inferiority test of proportions with α=0.05 following the principle of closed testing procedures. The proportion of patients who did not experience emesis, the proportion of patients who did not experience nausea, and the proportion of patients who did not need rescue medication were analyzed using a chi-square test. The severity of nausea was compared between the treatment groups using Kruskal–Wallis and Mann–Whitney tests. Time to first emetic episode was evaluated by Kaplan–Meier estimates and log-rank test. All safety data are presented using descriptive statistics.

Results

A total of 651 patients were enrolled; of these, 639 were available for safety analyses since 12 patients who received no study medication were excluded; four patients withdrew from the study (Fig. 1). Thus, 635 patients were available for efficacy analyses (FAS). Patient characteristics are summarized in Table 1.

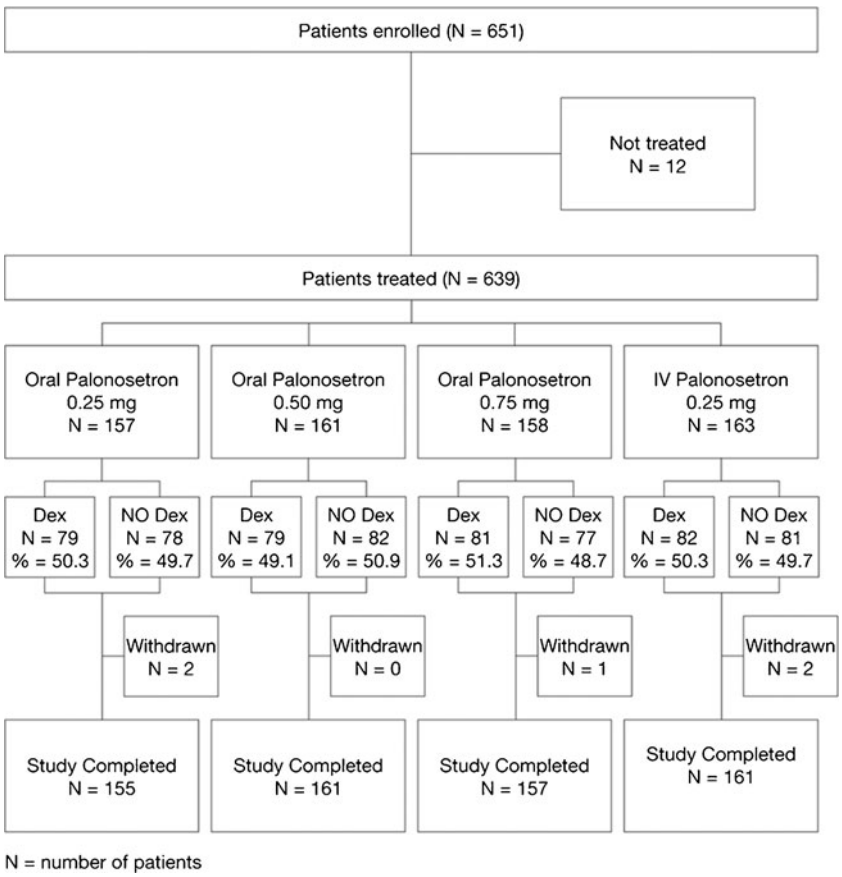

Fig. 1 CONSORT diagram

Table 1 Summary of patient characteristics (FAS)

	Oral palonosetron						IV palonosetron	
	0.25 mg (*N*=155)		0.50 mg (*N*=160)		0.75 mg (*N*=158)		0.25 mg (*N*=162)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age (years)	57.1	11.9	56.1	12.3	55.8	12.7	57.7	12.7
	n	%	*n*	%	*n*	%	*n*	%
Gender								
Male	40	25.8	42	26.3	44	27.8	45	27.8
Female	115	74.2	118	73.8	114	72.2	117	72.2
Ethnic group								
White	111	70.7	112	69.6	106	67.1	115	70.6
Black	2	1.3	1	0.6	2	1.3	0	0.0
Hispanic	43	27.4	45	28.0	49	31.0	45	27.6
Asian	1	.0.6	1	0.6	0	0.0	2	1.2
Other	0	0.0	2	1.2	1	0.6	1	0.6
Main cancer type								
Breast cancer	81	52.3	82	51.3	82	51.9	85	52.5
Colon cancer	11	7.1	8	5.0	12	7.6	7	4.3
Lung malignant neoplasm	8	5.2	8	5.0	4	2.5	12	7.4
Chemotherapy history								
Naïve	95	61.3	91	56.9	93	58.9	96	59.3
Non-naïve	60	38.7	69	43.1	65	41.1	66	40.7
Alcohol consumption								
No	101	65.2	86	53.8	88	55.7	94	58.0
Rarely	30	19.4	41	25.6	43	27.2	34	21.0
Occasionally	21	13.5	27	16.9	25	15.8	31	19.1
Regularly	3	1.9	6	3.8	2	1.3	3	1.9

N number of patients in a specific group, *n* number of patients in the relevant category, % percentage based on *N*, *SD* standard deviation

Efficacy

Complete response

The CR (defined as no emesis and no rescue medication) rates were generally similar in all treatment groups during the acute (0–24 h) and delayed (24–120 h) phases, as well as the overall 0–120 h time interval (Fig. 2). Non-inferiority between the oral palonosetron 0.50 mg and IV 0.25 mg groups was achieved in the acute and overall phases (acute: lower bound of 98.3 % CI was −6.5 %; overall: lower bound of 98.3 % CI was −14.2 %) but not in the delayed phase, where a difference in CR rates of 2.9 % was seen (lower bound of 98.3 % CI was −16.3 %; Table 2).

Similarly, in the acute phase (0–24 h), non-inferiority was achieved for the 0.25 mg (lower bound of 98.3 % CI was −8.9 %) oral doses and 0.75 mg (lower bound of 98.3 % CI was −8.9 %) for oral doses compared to the 0.25 mg IV formulation. In the delayed phase, none of the oral doses tested reached non-inferiority to the IV dose (0.25 mg oral: lower bound of 98.3 % CI was −19.7 %; 0.75 mg oral: lower bound of 98.3 % CI of −18.8 %). In the overall phase, among the oral doses, only the 0.50 mg oral dose was non-inferior to the 0.25 mg IV dose (0.25 mg oral: lower bound of 98.3 % CI was −19.6 %; 0.75 mg oral: bound of 98.3 % CI was −19.9 %).

Emetic episodes

The majority of patients in all treatment groups did not suffer from emesis, and the proportion of patients with no emetic episodes was similar across all treatment groups during all time intervals (Fig. 3). No emesis rates ranged from 77 to 83 % in the acute phase, 68–75 % in the delayed phase, and 61–70 % in the overall phase. The highest rate of protection from emesis among the oral doses was observed in the oral palonosetron 0.50 mg group for the acute, delayed, and overall periods. The highest difference in the percentage of patients with no emetic episodes in favor of oral palonosetron compared to IV palonosetron was seen

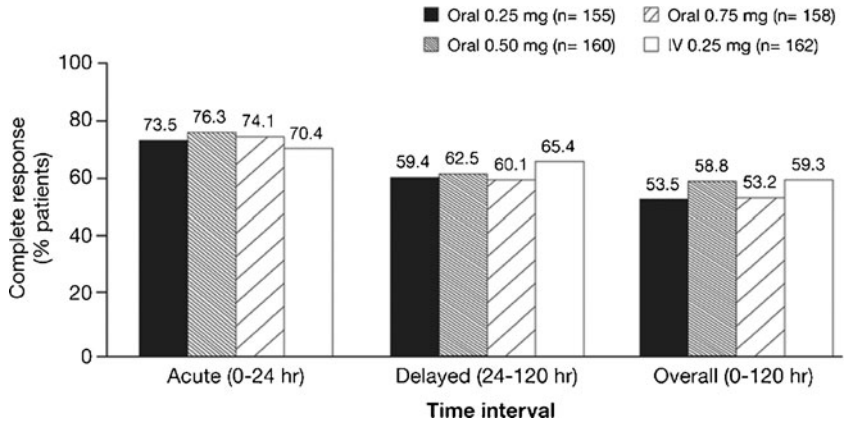

Fig. 2 Complete response rates during the acute, delayed, and overall phases of CINV (FAS, *N*=635). Non-inferiority was shown for oral palonosetron 0.50 mg vs IV palonosetron 0.25 mg for patients with no emesis in the acute, delayed, and overall phases

with the oral 0.50 mg dose during the acute phase. More than 50 % of patients experienced no emetic episodes throughout the 120-h time period.

Nausea

In the daily nausea assessment, the proportion of patients with no nausea was comparable across all treatment groups, with >78 % of patients having no more than mild nausea in the oral palonosetron 0.50 mg (82.8 %) and IV palonosetron 0.25 mg groups (78.6 %) on each day. No statistically significant difference was seen between oral palonosetron 0.50 mg vs IV palonosetron 0.25 mg for the proportion of patients with no nausea during the acute, delayed, and overall time intervals, as 58.8 vs 57.4 %, 49.4 vs 47.5 %, and 45.6 vs 42.6 %, respectively (p=0.807; p=0.740, p=0.583 in the acute, delayed, and overall phases).

Similarly, no statistically significant difference was seen in the comparisons between 0.25 mg oral and 0.25 mg IV palonosetron in the acute, delayed, and overall phases [respectively, 59.4 vs 57.4 % (p=0.725), 41.9 vs 47.5 % (p=0.316), 38.1 vs 42.6 % (p=0.411)] and between 0.75 mg oral vs 0.25 mg IV palonosetron in the acute [62.7 vs 57.4 % (p=0.337)], delayed [46.2 vs 47.5 % (p=0.811)], and overall phases [41.8 vs 42.6 % (p=0.681)] (Fig. 4).

Efficacy in subgroups with and without dexamethasone

In the acute phase, all patient subgroups receiving dexamethasone showed higher CR rates than the corresponding subgroups without dexamethasone (Table 2). In this phase, the highest CR rate in patients who received dexamethasone was seen in the oral 0.50 mg group (86.1 %). In the delayed phase, CR was higher in the subgroups with dexamethasone compared to the subgroups without dexamethasone, except for the 0.25 mg oral group. In the delayed phase, the differences between the two subgroups with and without dexamethasone were less pronounced than in the acute phase. Of note, the 0.25 mg oral group was the only group to show a gain of <15 % in CR in the acute phase with the addition of dexamethasone and was the only group to not show a gain

Table 2 Complete response rates in patients with or without concomitant dexamethasone (FAS)

			Oral palonosetron			IV palonosetron
			0.25 mg (*N*=155) % [95 % CI]	0.50 mg (*N*=160) % [95 % CI]	0.75 mg (*N*=158) % [95 % CI]	0.25 mg (*N*=162) % [95 % CI]
0–24 h	Total		73.5 [65.8, 80.2]	76.3 [68.8, 82.5]	74.1 [66.4, 80.5]	70.4 [62.7, 77.1]
	DEX	Yes[a]	76.9 [65.8, 85.4]	86.1 [76.0, 92.5]	85.0 [74.9, 91.7]	82.9 [72.7, 90.0]
		No[b]	70.1 [58.5, 79.8]	66.7 [55.2, 76.5]	62.8 [51.1, 73.3]	57.5 [46.0, 68.3]
24–120 h	Total		59.4 [46.7, 62.8]	62.5 [50.7, 66.4]	60.1 [46.3, 62.3]	65.4 [52.5, 68.0]
	DEX	Yes[a]	57.7 [46.0, 68.6]	63.3 [51.6, 73.6]	63.8 [52.2, 74.0]	68.3 [57.0, 77.9]
		No[b]	61.0 [49.2, 71.7]	61.7 [50.2, 72.1]	56.4 [44.7, 67.4]	62.5 [50.9, 72.9]
0–120 h	Total		53.5 [45.4, 61.5]	58.8 [50.7, 66.4]	53.2 [45.1, 61.1]	59.3 [51.3, 66.8]
	DEX	Yes[a]	52.6 [41.0, 63.9]	63.3 [51.6, 73.6]	58.8 [47.2, 69.5]	65.9 [54.5, 75.7]
		No[b]	54.5 [42.8, 65.8]	54.3 [42.9, 65.3]	47.4 [36.1, 59.0]	52.5 [41.1, 63.7]

[a] *N*=319 with dexamethasone

[b] *N*=316 without dexamethasone

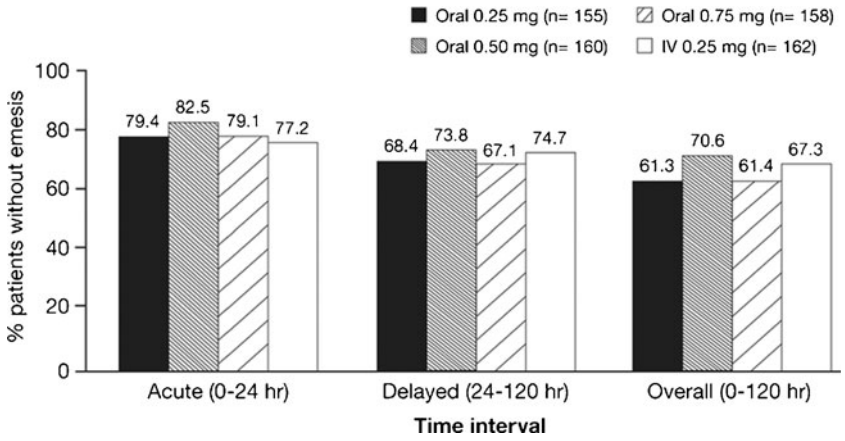

Fig. 3 Proportion of patients with no emetic episodes in the different treatment arms during the acute, delayed, and overall phases of CINV (FAS, *N*=635)

in CR in the delayed phase or overall phase with the addition of dexamethasone (Table 2).

Due to the similar efficacy of the three oral doses tested, the oral data were pooled and compared to IV palonosetron with and without dexamethasone. In the acute period, in the oral and IV groups, CR rates with dexamethasone were 82.7 and 82.9 %, respectively, compared to 66.5 and 57.5 % without dexamethasone, respectively. In the delayed period, in the oral and IV groups, CR rates were 61.6 and 68.3 %, respectively, with dexamethasone, vs 58.7 and 62.5 %, respectively, without dexamethasone. Finally, in the overall period, CR rates were 58.2 and 65.9 % with dexamethasone and 52.1 and 52.5 % without dexamethasone, respectively, in the pooled oral and IV groups. Thus, a similar trend for IV and oral palonosetron was seen, with a clinical advantage when dexamethasone was added, mainly during the acute phase.

Rescue medication

Consistent with the no emesis and no nausea results, the percentage of patients using antiemetic rescue medication in the 0.25, 0.50, and 0.75 mg oral groups was similar: 30.3 % (*n*=47), 29.4 % (*n*=47), and 31.0 % (*n*=49), respectively, compared to 29.0 % (*n*=47) in the IV palonosetron group.

Safety

The percentage of patients with treatment-emergent adverse events was comparable in all four treatment groups (47–50 %), with no dose response relationship noted for the oral palonosetron groups. Treatment-related (possibly/probably related) adverse events were reported with similar frequencies in the three oral palonosetron groups (7.0, 8.1, and 7.6 % of patients for the 0.25, 0.50, and 0.75 mg doses, respectively), while a higher percentage of patients with related adverse events was seen in the IV palonosetron group (16.0 % of patients). The most common treatment-related adverse event in all treatment groups was headache, which was comparable for its frequency in the three oral palonosetron groups (0.25 mg, 3.8 %; 0.50 mg, 3.7 %; 0.75 mg, 3.8 %), but slightly higher in the IV palonosetron group (8.6 %). Additionally, constipation was among the most frequently reported treatment-related adverse event in the oral 0.75 and 0.25 mg IV groups (3.2 and 3.1 %, respectively) compared to the oral 0.25 and 0.50 mg groups (0.6 % in each group).

Regardless of the relationship to the study drug, the majority of the adverse events reported in this study did not exceed mild intensity in all treatment groups. The type and severity of adverse events were similar for the oral

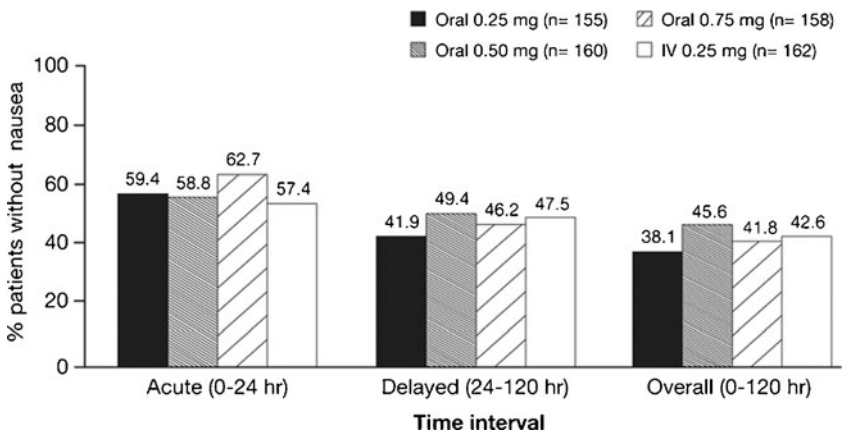

Fig. 4 Proportion of patients with no nausea in the different treatment arms during the acute, delayed, and overall phases of CINV (FAS, *N*=635)

palonosetron and IV groups, and were typical for the 5-HT_3RA class.

Three adverse events led to withdrawal of two patients from the study. One adverse event (thrombocytopenia, mild, unrelated) occurred in the oral palonosetron 0.50 mg group; two adverse events were serious and occurred in the 0.75 mg treatment group (febrile neutropenia and septic shock, both severe and fatal and unrelated to the study drug). There was only one serious adverse event, assessed by the investigator as being related to the study drug, in a patient who was diagnosed with a chronic left bundle branch block at baseline detected by ECG before any intake of study medication. The same cardiac abnormality seen at baseline was seen 3 h after administration of the study drug. The patient recovered after hospitalization and pacemaker implantation.

No clinically relevant differences were observed between the three oral palonosetron groups and the IV palonosetron treatment group with regard to laboratory parameters, vital signs, and 12-lead ECG. Possibly related ECG adverse events were reported in ≤1.2 % of patients in all four treatments groups. No pronounced differences were observed between the four treatments concerning hematology or blood chemistry parameters, or their changes during the study.

Discussion

Both oral and IV formulations of first-generation 5-HT_3 RAs are effective, as reflected in current antiemetic guidelines [7–9]. Similarly, the three oral palonosetron doses administered in this dose-ranging study (0.25, 0.50, and 0.75 mg) demonstrated consistent prevention of CINV across several efficacy endpoints, as previously demonstrated for IV palonosetron 0.25 mg [3, 5, 6]. Efficacy results in the 0–24-h period (acute phase) were not directly related to the predicted plasma concentrations of palonosetron. Indeed, all of the oral tested doses were non-inferior to the 0.25 mg IV formulation in the acute phase. Similar results were also seen during the 0–120-h interval (overall phase). During the delayed phase, CR rates were highest in the IV palonosetron group followed by the 0.50, 0.75, and 0.25 mg oral dose groups. Although statistical non-inferiority was not achieved in the pre-specified analysis in the delayed phase for any of the oral doses, the absolute difference in CR rate between the oral 0.50 mg dose and the IV 0.25 mg dose was only 2.9 %.

Although no clear dose response trends or significant differences were seen between the oral doses, the 0.50 mg oral dose demonstrated numerically higher antiemetic efficacy rates compared to the other oral treatment arms in the acute, delayed, and overall periods. Moreover, the 0.50 mg dose was the only dose to show non-inferiority vs IV in the overall CR. There were no significant differences between any of the oral palonosetron treatment groups and the IV group for the secondary endpoints of protection from emesis, level of nausea, or use of rescue medication.

Administration of a single dose of dexamethasone with palonosetron on day 1 led to substantially higher CR rates during the acute phase in the oral 0.50 mg, oral 0.75 mg, and IV 0.25 mg palonosetron groups. The additional efficacy obtained with dexamethasone was less pronounced in the delayed phase. Of note, the added benefit of dexamethasone was lesser in magnitude in the oral 0.25 mg group, suggesting that palonosetron 0.50 mg may be the lowest oral dose for which full benefit is seen. Due to the similar efficacy of the three oral doses tested, the data were pooled, and comparison of all the oral-treated patients with dexamethasone confirmed the analysis of single oral doses vs the IV formulation.

The safety profile of oral palonosetron was similar to that of IV palonosetron in terms of overall frequency and intensity of adverse events. However, headache was seen less frequently with oral palonosetron, and constipation was somewhat less frequent with the lower doses of oral palonosetron. Analysis of adverse events, laboratory values, vital signs, and 12-lead ECGs did not raise any safety concerns for the administration of palonosetron as a single oral dose. Concomitant dexamethasone did not introduce substantial differences in the safety profiles compared to the subgroups without dexamethasone.

Similar efficacy was found at all three oral doses compared to IV administration of palonosetron. However, the 0.50 mg oral dose showed numerically superior efficacy without a tolerability disadvantage. Considering the overall efficacy and tolerability profile of oral palonosetron with or without dexamethasone, oral palonosetron 0.50 mg can be considered an acceptable therapeutic option for the prevention of CINV from moderately emetogenic chemotherapy in settings where an oral formulation is preferred.

Conflict of interest Financial disclosures: Ralph Boccia, Edwin Franco, Edward Rubenstein, and Steven Grunberg have no financial disclosures or potential conflicts of interest to report. Daniel Voisin is an employee at Helsinn Healthcare and was also at Helsinn at the time the study was conducted. The authors have control of all primary data and agree to allow the journal to review the data if requested.

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