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Multicenter phase IV study of palonosetron in the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients with non-Hodgkin lymphomas undergoing repeated cycles of moderately emetogenic chemotherapy

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Abstract

Antiemetic therapy for chemotherapy-induced nausea and vomiting in patients with non-Hodgkin lymphoma (NHL) receiving moderately emetogenic chemotherapy (MEC) generally includes a serotonin-type 3 (5-HT_3) receptor antagonist (RA). The efficacy and safety of the second-generation 5-HT_3 RA, palonosetron, in patients with NHL receiving MEC was assessed. Patients received a single iv bolus injection of 0.25 mg palonosetron and chemotherapy on day 1 of the first chemotherapy cycle, and up to three further consecutive cycles. Eighty-eight patients were evaluable for efficacy and safety. The primary endpoint, the percentage of patients with a complete response in the overall phase (0–120 h after chemotherapy in each cycle), increased from 68.2% (cycle 1) to 80.5% (cycle 2), remaining high for the following cycles, and >90% patients were emesis-free without using aprepitant during therapy. Across all cycles, 78.4% of patients experienced treatment-emergent adverse events, but only 8% related to study drug, confirming palonosetron's good safety profile (EudraCT Number: 2008-007827-14).

Keywords: Palonosetron, emetogenic chemotherapy, serotonin-type 3 receptor antagonist, 5-HT_3 RA, chemotherapy-induced nausea and vomiting, CINV

Introduction

Chemotherapy-induced nausea and vomiting (CINV) adversely affects patient quality of life (QoL) and often leads to treatment discontinuation, particularly in patients receiving repeated cycles of therapy. Thus, control of CINV is crucial not only to the successful delivery of planned therapy in patients with cancer receiving emetogenic chemotherapy agents, but also to patient well-being. Helpfully, guidelines have defined the emetic risk of various single chemotherapy agents, administered either intravenously or orally [1], as high, moderate, low and minimal, corresponding to a risk of emesis in >90%, 30–90%, 10–30% and <10% of patients, respectively, in the absence of prophylactic antiemetic protection. Typically, prophylaxis for highly emetogenic chemotherapy (HEC) regimens comprises a combination of a 5-hydroxytryptamine (5-HT_3) receptor antagonist (RA), dexamethasone and a neurokinin-1 (NK_1) receptor antagonist, whilst that for moderately emetogenic chemotherapy (MEC) comprises a 5-HT_3 RA and either dexamethasone or methylprednisone.

Palonosetron (Aloxi®, Oncit®, Paloxi®), a second-generation, serotonin-type 3, 5-HT_3 RA indicated for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderate to highly emetogenic cancer chemotherapy, is distinguished from other 5-HT_3 RAs by its prolonged half-life (~40 h), high binding affinity (~2500-fold higher than serotonin) and its distinct mechanism of action including allosteric binding, positive cooperativity and receptor internalization [2,3].

Palonosetron has demonstrably better efficacy than the first-generation 5-HT_3 RAs ondansetron and dolasetron in the prevention of CINV in patients receiving MEC [4,5], and similar efficacy to ondansetron in preventing CINV in patients receiving HEC [6]. Furthermore, in a meta-analysis of five randomized studies of patients receiving MEC or HEC, palonosetron was shown to be more effective than other 5-HT_3 RAs in the prevention of acute (0–24 h post-chemotherapy) and delayed (24–120 h post-chemotherapy) phase CINV in patients receiving moderately and highly emetogenic therapies [7]. Palonosetron has been shown to be non-inferior to granisetron in the acute phase and superior to granisetron in the delayed phase in the prevention of CINV when administered with dexamethasone prior to HEC in Japanese patients [8]. Palonosetron has also been shown to be effective in managing nausea and vomiting induced by a variety of chemotherapeutic agents across a range of

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indications [9–17], including hematological malignancies, where patients are at particular risk of CINV [18,19], and specifically in the treatment of patients with non-Hodgkin lymphoma (NHL) [20].

Antiemetic therapy for patients with lymphoma receiving chemotherapy generally consists of a 5-HT_3 RA and dexamethasone [21–23]. However, recent studies have demonstrated that the use of palonosetron may be of benefit in reducing or minimizing the recommended use of steroids [9,12,13]. The aim of this multicenter single-arm phase IV trial was to extend the findings of the previous study of palonosetron in patients with NHL [20], and to assess the efficacy of single doses of 0.25 mg intravenous (iv) palonosetron during an individual study cycle and the maintenance of such efficacy through repeated and consecutive study cycles, in patients with NHL receiving a minimum of two and up to a maximum of four repeated consecutive cycles of MEC administered on a single day.

The safety of iv palonosetron administered on day 1 of the initial and repeated consecutive MEC cycles for up to four study cycles was also evaluated.

Methods

This study (EudraCT Number: 2008-007827-14) was a multicenter, open label, uncontrolled, phase IV study to assess the efficacy and safety of single doses of 0.25 mg iv palonosetron administered on day 1 of consecutive study cycles in patients with NHL receiving MEC. The study was conducted according to the Declaration of Helsinki and Good Clinical Practice Guidelines in centers in the United States and Europe, with each center enrolling at least one patient. The protocol was approved by the local ethics committees, and all patients provided written informed consent to their participation in the study.

Chemo-naive, male and female patients $\geq$ 18 years of age with histologically confirmed NHL (any stage) and a Karnofsky performance status of $\geq$ 50% scheduled to receive one of the following MEC regimens, namely CHOP or R-CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone, plus or minus rituximab) or ProMACE-CytaBOM (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate, leucovorin and prednisone) were eligible for inclusion. Additional inclusion criteria included acceptable cardiac, hepatic and renal function, although patients with a known hepatic, renal or cardiovascular impairment, including cardiac conduction interval abnormalities, could be enrolled (or continue their participation in the repeated study cycles) at the discretion of the investigator.

Patients were not to have taken any antiemetic medication within the 24 h prior to administration of the study medication or to have experienced vomiting, retching or National Cancer Institute (NCI) common toxicity grade 2 or 3 nausea, in the 24 h prior to therapy. Treatment with commercial palonosetron was forbidden during the 2 weeks prior to study drug administration.

Treatment

Palonosetron was administered at a dose of 0.25 mg as a 30 s iv bolus injection, 30 min prior to administration of the first emetogenic chemotherapy agent of the MEC regimen on day 1, cycle 1 and on day 1 of each subsequent consecutive MEC cycle. MEC was to be administered on day 1 of each cycle only.

Patients attended their study center on three occasions for each study cycle: visit 1, the screening visit (days -15 to -1 in cycle 1; days -3 to 1 for subsequent cycles), visit 2 (day 1) and visit 3 (days 8–10). Patients were to participate for a minimum of two and a maximum of four consecutive study cycles. In addition to study treatment, rescue medication for the treatment of nausea and vomiting was allowed after the start of administration of the first emetogenic agent, at the discretion of the investigator. The choice of rescue antiemetic agent was also at the discretion of the investigator; however, the use of 5-HT_3 RAs was discouraged. The use of palonosetron was not permitted.

Study objectives

The principal objective of the study was to assess the efficacy of single doses of iv palonosetron 0.25 mg administered on day 1 of individual study cycles and the maintenance of such efficacy through repeated and consecutive study cycles in the prevention of CINV in patients with NHL receiving MEC administered over a single day. The primary endpoint was the overall complete response (CR) rate, defined as no emetic episode and no rescue medication for the overall phase after the start of emetogenic chemotherapy. Secondary efficacy endpoints were the CR rates for acute and delayed phases, the severity of nausea, the percentage of patients with complete protection (CP, defined as no vomiting, no rescue therapy and no nausea), the percentage of patients without emesis and the percentage of patients without rescue medication for the acute, delayed and overall phases. Time to treatment failure (TTF), defined as the time to the first emetic episode or administration of rescue medication, whichever occurred first, was also recorded. The impact of palonosetron on QoL using the modified Functional Living Index-Emesis (FLIE) questionnaire was also investigated [24].

Secondary objectives included evaluation of the safety of iv palonosetron 0.25 mg in initial and repeated, consecutive cycles of MEC, for up to four cycles, with the assessment of adverse events (AEs), laboratory parameters, vital signs, physical examinations and 12-lead electrocardiograms (ECGs). Safety characteristics were documented throughout the study, with patients monitored for the occurrence of AEs at each study visit or contact (day 1 [visit], day 2 [telephone contact], days 8–10 [visit]) of each cycle. AEs were classified as mild, moderate or severe by the investigator. Severe AEs were defined as those causing severe discomfort and that may be of such severity that the patient could not continue in the study. Single 12-lead ECGs were taken before the first administration of study drug, day 1 of cycle 1 and post-dosing at visit 3 of each subsequent study cycle.

Patients were asked to fill in a diary for days 1–5 of each treatment cycle. All efficacy endpoints were based on diary data. The patient's diary collected daily interval (0–24 h, $>$ 24–48 h, $>$ 48–72 h, $>$ 72–96 h, $>$ 96–120 h) assessments of nausea severity measured using a 100 mm horizontal visual analog scale (VAS) as well as any experience of

retching/vomiting and rescue medication intake during the 0–120 h interval after administration of the first emetogenic chemotherapy for each study cycle. The VAS scores (in mm) for nausea were categorized as follows: <5 no nausea, $5 \leq 25$ no significant nausea, ≥ 25 nausea.

The FLIE data were collected only on the fifth day of each cycle. Thus, the QoL assessment was analyzed according to the cycle in which it was performed (cycles 1–4) rather than daily.

Statistics

Initially, the enrollment of 200 patients was planned. However, due to enrollment difficulties and to the approaching study medication expiry date of 30 April 2011, it was decided that study enrollment should be stopped on 31 January 2011. Based on an updated estimated sample size of 100 patients and the assumption of a CR rate of 75% during the 0–120 h time interval, recalculation of the two-sided exact 95% confidence interval (CI) resulted in a two-sided exact 95% CI of [66.5%, 83.5%] for each study cycle.

The full analysis set (FAS) for the determination of efficacy was defined as those patients who had received at least one cycle of MEC with 0.25 mg iv palonosetron. Cycles without administration of at least MEC and/or study drug were excluded from the analysis. Results for the FAS were interpreted in a descriptive manner with 95% CIs. Subgroup analyses were provided for all efficacy parameters by region, gender and age group (<65 years, ≥ 65 years). Kaplan–Meier curves were used to assess the TTF.

The safety population included all patients who had received at least one cycle of MEC with 0.25 mg iv palonosetron and for whom at least one post-treatment safety assessment was available. MEC cycles without administration of palonosetron and/or without post-treatment safety assessment were excluded from the analysis. AEs were coded using The Medical Dictionary for Regulatory Activities (MedDRA) version 12.0, to provide a system organ class (SOC) and preferred term (PT) for each event. Subgroup analyses of AE tables by region, age group and gender were performed. Clinical laboratory data were summarized using frequency tables for values within/outside reference ranges and shift tables were used to evaluate changes in clinical laboratory data versus baseline.

Role of the funding source

The study sponsor, Helsinn Healthcare SA, was involved in the study design, the collection, analysis and interpretation of the data via a Helsinn Healthcare sponsored CRO, and in the decision to publish.

Results

Between 20 January 2010 and 31 January 2011, 88 male and female patients with NHL were enrolled by 18 centers in the USA and Europe (five in the USA, four in the Czech Republic, four in Romania, three in Italy and two in Germany). Eighty-eight patients were treated with at least one cycle of MEC. Of these, 68 patients (77.3%) completed the study, while 20 patients (22.7%) terminated the study early: seven (8.0%) due to early termination of the entire study, three (3.4%) due to AEs, two (2.3%) each due to death, withdrawal of consent and change in chemotherapy, and one (1.1%) each due to protocol violation, lost to follow-up, sponsor decision and other reason. Overall, 68 patients (77.3%) completed the study, receiving four therapy cycles, 10 patients (11.4%) completed three cycles of therapy, three patients (3.4%) completed two cycles of therapy and seven patients (8.0%) completed only one cycle of therapy.

All 88 patients were eligible for inclusion in both the efficacy and safety analysis sets. All patients were eligible for subgroup analysis. The demographic data and patient baseline characteristics are summarized in Table I.

The majority of patients, median age 61.5 years, were white (98.9%) males (60.2%), and all but one patient received CHOP plus or minus rituximab (98.9%) MEC. The remaining patient received ProMACE-CytaBOM MEC (Table I). Almost 91% of patients had B-cell NHL. The time from diagnosis of NHL ranged from less than 1 week (12.5% of patients) to at least 8 weeks (17.0% of patients). At least one concomitant disease/medical condition was noted for 86.4% of patients, with those most frequently reported being vascular disorders (38.6%; mainly hypertension), metabolism and nutrition disorders (22.7%) and musculoskeletal and connective tissue disorders (20.5%) (data not shown).

Efficacy

Patients received palonosetron for a total of 317 cycles of MEC (mean 3.6; median 4). Overall, CR was observed for 76.7% [95% CI: 71.7, 81.0] of treatment cycles. During the overall phase the percentage of patients with a CR increased from 68.2% [95% CI: 57.9, 77.0] for cycle 1 to 80.5% [95% CI: 70.6, 87.6] for cycle 2 and essentially remained the same for the following two cycles (Table II). During all cycles, the percentage of patients with a CR was lower for the 0–24 h

Table I. Patient characteristics.

Characteristic	Patients ($N = 88$)
Age (years)	
Median (range)	61.5 (29–89)
Age group, *n* (%)	
<65 years	53 (60.2)
≥ 65 years	35 (39.8)
Gender, *n* (%)	
Male	53 (60.2)
Female	35 (39.8)
Karnofsky performance status†	
Median (range)	90.0 (50–100)
Race, *n* (%)	
White	87 (98.9)
Hispanic	1 (1.1)
Diagnosis of non-Hodgkin lymphoma	88 (100)
Chemotherapy regimen	
CHOP	41 (46.6)
R-CHOP (after)*	32 (36.4)
R-CHOP (before)†	14 (15.9)
ProMACE-CytaBOM	1 (1.1)

n, number of patients in specified treatment group; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ProMACE-CytaBOM, prednisone, doxorubicin, cyclophosphamide, etoposide, cytarabine, bleomycin, vincristine, methotrexate plus leucovorin; R-CHOP, rituximab–CHOP; MEC, moderately emetogenic chemotherapy.

*R-CHOP (after): regimen with rituximab after study drug administration and MEC, day 1.

†R-CHOP (before): regimen with rituximab before study drug administration and MEC, day 1.

Table II. Number and percentage of patients with a complete response, by study cycle and overall.

	Cycle 1 ($N = 88$)		Cycle 2 ($N = 82$)		Cycle 3 ($N = 78$)		Cycle 4 ($N = 69$)		Total ($N = 317$)	
Day(s)/interval, h	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Overall, 0–120	60	(68.2)	66	(80.5)	61	(78.2)	56	(81.2)	243	(76.7)
Delayed phase, > 24–120	73	(83.0)	77	(93.9)	72	(92.3)	65	(94.2)	287	(90.5)
Day 1, 0–24	68	(77.3)	69	(84.1)	64	(82.1)	58	(84.1)	259	(81.7)
Day 2, > 24–48	77	(87.5)	79	(96.3)	75	(96.2)	67	(97.1)	298	(94.0)
Day 3, > 48–72	80	(90.9)	80	(97.6)	76	(97.4)	66	(95.7)	302	(95.3)
Day 4, > 72–96	84	(95.5)	80	(97.6)	76	(97.4)	67	(97.1)	307	(96.8)
Day 5, > 96–120	82	(93.2)	78	(95.1)	74	(94.9)	67	(97.1)	301	(95.0)

interval (acute phase) than for the subsequent daily intervals. In the delayed phase, the percentage of patients with a CR increased from 83.0% [95% CI: 73.8, 89.4] for cycle 1 to 93.9% [95% CI: 86.5, 97.4] for cycle 2, with similar proportions of complete responders for cycles 3 and 4. The average percentage of complete responders over all cycles for the delayed phase was 90.5% [95% CI: 86.8, 93.3].

For both the acute and delayed phases, the majority of patients with a CR in the first cycle also showed a CR in subsequent cycles. For example, of the 68 patients who were complete responders in the acute phase of cycle 1 (Table II), only two were non-responders in cycle 2, whilst six of the 20 non-responding patients in cycle 1 were responders in cycle 2. There were 11 patients who were non-responders in both cycles and six patients who did not contribute to cycle 2 (no longer participated in the study). For the delayed phase, the majority of patients with a CR in the first cycle also showed a CR in subsequent cycles. Overall the percentage of patients with a CR increased in cycles 2–4 compared with cycle 1.

For the acute phase, across all cycles, the mean severity of nausea on the VAS was 5.6 mm, corresponding to "no significant nausea." Similarly, in the delayed phase, the patients' mean severity of nausea was 4.37 mm across all cycles ("no nausea"). Using the patients' maximum values, the mean severity of nausea decreased from 11.34 mm for cycle 1 to 5.19 mm for cycle 4 (no significant nausea). For the entire 0–120 h interval, the patients' mean severity of nausea decreased from 7.03 mm in cycle 1 to 4.08 mm in cycle 2, and stayed relatively stable thereafter. The proportion of cycles in which patients had nausea in any of the three defined phases (acute, delayed and overall) is summarized in Table III.

Table IV summarizes the CP, emesis-free and no rescue medication rates across all cycles. Complete protection was achieved in 79.2% [95% CI: 74.4, 83.3], 86.4% [95% CI: 82.2, 89.8] and 72.2% [95% CI: 67.1, 76.9] of all cycles during the acute, delayed and overall phases, respectively. In the acute phase the percentage of patients with CP increased from cycle 1 to cycle 2 and showed similar values for cycles 3 and 4. An even higher increase was seen in the delayed phase, where the percentage of patients showing CP increased from 76.1% [95% CI: 66.3, 83.8] in cycle 1 to 91.5% [95% CI: 83.4, 95.8] in cycle 2, and remained > 10% higher than in cycle 1 for the subsequent two cycles. For the overall phase, the percentage of patients showing CP increased by > 10% from cycle 1 to cycle 2, and again remained high in cycles 3 and 4.

A similar pattern was observed for patients without emesis and for patients not using rescue medication (Table IV). No emesis was observed in 90.5% [95% CI: 86.8, 93.3] of all cycles, and no rescue medication was used in 81.7% [95% CI: 77.1, 85.6] of all cycles. The total score obtained from assessments using 100 mm VAS and point scores in the modified FLIE for nausea and vomiting showed only little difference across the individual cycles.

Safety

The safety of palonosetron 0.25 mg was assessed for each evaluable study cycle ($n = 314$). All 88 patients were evaluable for safety. Only treatment-emergent AEs (TEAEs) were considered. These were defined as all AEs that occurred after the first administration of study medication.

Overall, 78.4% of patients experienced 301 TEAEs. A total of 17 patients (19.3%) experienced 26 serious TEAEs. None of the serious TEAEs were considered to be study-drug related (Table V).

A relationship between TEAEs and study drug was reported for only 8.0% of all patients. Only 4.5% of all patients had

Table III. Nausea scores by category and cycle.

		Cycle 1 ($N = 88$)		Cycle 2 ($N = 82$)		Cycle 3 ($N = 78$)		Cycle 4 ($N = 69$)		Total ($N = 317$)	
Phase/interval, h	Nausea, mm†	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
Acute, 0–24	< 5	69	(78.4)	63	(76.8)	61	(78.2)	61	(88.4)	254	(80.1)
	5 ≤ 25	14	(15.9)	14	(17.1)	14	(17.9)	4	(5.8)	46	(14.5)
	≥ 25	5	(5.7)	5	(6.1)	3	(3.8)	4	(5.8)	17	(5.4)
Delayed, > 24–120 (max)*	< 5	54	(61.4)	62	(75.6)	62	(79.5)	55	(79.7)	233	(73.5)
	5 ≤ 25	21	(23.9)	16	(19.5)	13	(16.7)	9	(13.0)	59	(18.6)
	≥ 25	13	(14.8)	4	(4.9)	3	(3.8)	5	(7.2)	25	(7.9)
Overall, 0–120 (max)*	< 5	49	(55.7)	59	(72.0)	56	(71.8)	54	(78.3)	218	(68.8)
	5 ≤ 25	24	(27.3)	16	(19.5)	17	(21.8)	9	(13.0)	66	(20.8)
	≥ 25	15	(17.0)	7	(8.5)	5	(6.4)	6	(8.7)	33	(10.4)

VAS, visual analog scale.
*Patients' maximum values during given time interval.
†VAS scores (in mm) were categorized as: < 5: no nausea, 5 ≤ 25: no significant nausea, ≥ 25: nausea.

Table IV. Complete protection, emesis-free and no rescue medication rates by cycle.

	Cycle 1 (N^* = 88)		Cycle 2 (N = 82)		Cycle 3 (N = 78)		Cycle 4 (N = 69)		Total (N = 317)	
Phase/interval, h	n^*	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Complete protection										
Acute, 0–24	67	(76.1)	66	(80.5)	62	(79.5)	56	(81.2)	251	(79.2)
Delayed, >24–120	67	(76.1)	75	(91.5)	70	(89.7)	62	(89.9)	274	(86.4)
Overall, 0–120	55	(62.5)	64	(78.0)	57	(73.1)	53	(76.8)	229	(72.2)
No emesis										
Acute, 0–24	80	(90.9)	77	(93.9)	75	(96.2)	65	(94.2)	297	(93.7)
Delayed, >24–120	78	(88.6)	78	(95.1)	73	(93.6)	66	(95.7)	295	(93.1)
Overall, 0–120	76	(86.4)	75	(91.5)	72	(92.3)	64	(92.8)	287	(90.5)
No rescue medication										
Acute, 0–24	73	(83.0)	72	(87.8)	67	(85.9)	59	(85.5)	271	(85.5)
Delayed, >24–120	79	(89.8)	79	(96.3)	76	(97.4)	67	(97.1)	301	(95.0)
Overall, 0–120	67	(76.1)	69	(84.1)	66	(84.6)	57	(82.6)	259	(81.7)

*N, number of cycles; n, number of cycles with data available. Percentages are based on N. It should be noted that for each cycle (1, 2, 3 and 4), N and n are also equal to the number of patients in that cycle and to the number of patients with data available in that cycle, respectively.

TEAEs that were possibly related, and 3.4% of all patients had TEAEs that were probably related to study drug. The overall incidence of patients with TEAEs decreased continuously from cycle 1 to cycle 4, with the greatest decrease observed between cycles 2 and 3 (Table V). For those patients reporting study drug-related TEAEs, the highest incidence was observed in cycle 1, followed by cycle 4 and cycle 2, whilst the percentage of patients with serious TEAEs was highest for cycle 1, followed by cycle 3. At most, 5.7% of all patients had study drug-related TEAEs during any one cycle (Table V), and 8% of patients had drug-related TEAEs at any time during the study.

Overall, the most commonly reported TEAEs were those of the blood and lymphatic SOC (42.0% of patients), followed by gastrointestinal disorders (38.6% of patients) and infections and infestations (23.9% of patients). At the PT level, anemia and neutropenia (each occurring in 20.5% of patients), leukopenia (17.0% of patients), constipation (12.5% of patients) and alopecia (11.4% of patients) were the most frequent events.

The most important study drug-related TEAEs occurring in ≥2% of patients for the overall study period are summarized by patient in Table VI. These are constipation and fatigue (2.3% each). Headache, chills and peripheral neuropathy were experienced by 1.1% of patients each. Female patients experienced more TEAEs than male patients (91.4% vs. 69.8%), and the elderly had a higher incidence of TEAEs than younger patients.

Hematology, blood chemistry and laboratory values were normal at both baseline and visit 3 for the majority of cycles. Differences between the individual cycles and changes from baseline to visit 3 for systolic and diastolic blood pressure and pulse rate were small for all three parameters. The majority of ECG results were normal at baseline and at visit 3 of each cycle. Of the changes from normal at baseline to abnormal at visit 3, most were assessed to be not clinically significant. No clinically relevant arrhythmias or QT elongations were observed in this study.

Discussion

The efficacy of the administration of single-dose palonosetron has been demonstrated previously in the control of CINV, in patients with aggressive NHL receiving MEC regimens containing steroids over a single treatment cycle [20]. The present multicenter study confirms the published evidence

Table V. Summary of TEAEs by cycle.

	Cycle 1 (N^* = 88)			Cycle 2 (N = 81)			Cycle 3 (N = 77)			Cycle 4 (N = 68)		
Category	n^*	(%)	n'^*	n	(%)	n'	n	(%)	n'	n	(%)	n'
Cycles with at least one												
TEAE	51	(58.0)	125	44	(54.3)	74	29	(37.7)	58	22	(32.4)	44
Non-related TEAE	48	(54.5)	116	42	(51.9)	72	29	(37.7)	58	22	(32.4)	41
Drug-related TEAE†	5	(5.7)	9	2	(2.5)	2	0	(0.0)	0	3	(4.4)	3
Patients who died in the cycle	1	(1.1)		0	(0.0)		1	(1.3)		0	(0.0)	
Cycles with at least one												
Severe TEAE	8	(9.1)	16	6	(7.4)	7	4	(5.2)	6	1	(1.5)	2
Severe drug-related TEAE†	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Non-serious TEAE	50	(56.8)	111	43	(53.1)	71	29	(37.7)	51	22	(32.4)	42
Serious TEAE	9	(10.2)	14	2	(2.5)	3	5	(6.5)	7	2	(2.9)	2
Serious drug-related TEAE†	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
TEAE leading to study discontinuation	2	(2.3)	4	0	(0.0)	0	3	(3.9)	5	0	(0.0)	0
Drug-related TEAE leading to study discontinuation†	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0	0	(0.0)	0
Serious TEAE leading to study discontinuation	2	(2.3)	2	0	(0.0)	0	2	(2.6)	2	0	(0.0)	0

TEAE, treatment-emergent adverse event.
*N, number of cycles; n, number of cycles with at least one event in the category; n', number of events in the category. It should be noted that a patient could have had findings in more than one category, in a given cycle, and that for each cycle (1, 2, 3 and 4), N and n are also equal to the number of patients in that cycle and to the number of patients with data available in that cycle, respectively.
†TEAEs which the investigator considered to have a possible, probable, definite, unassessable or missing (if any) relationship to study medication.

Table VI. Study drug-related TEAEs* by system organ class and preferred term for the overall study period occurring in ≥ 2% of patients.

	$N = 88$		
SOC and PT (MedDRA, version 12.0)	*n*	(%)	*n'*
Patients with at least one drug-related TEAE	7	(8.0)	14
Gastrointestinal disorders	2	(2.3)	2
Constipation	2	(2.3)	2
General disorders and administration site conditions	3	(3.4)	4
Chills	1	(1.1)	1
Fatigue	2	(2.3)	3
Nervous system disorders	2	(2.3)	2
Headache	1	(1.1)	1
Peripheral sensory neuropathy	1	(1.1)	1

TEAE, treatment-emergent adverse event; SOC, system organ class; PT, preferred term; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients; *n,* number of patients with at least one event in the category; *n'*, number of events.
*It should be noted that drug-related TEAEs were TEAEs which the investigator considered to a have a possible, probable, definite, unassessable or missing (if any) relationship to study medication.

of the efficacy of a single iv dose of 0.25 mg palonosetron in individual study cycles, and extends the observation to the maintenance of efficacy through repeated and consecutive MEC cycles in which palonosetron is administered on day 1 of the cycle in patients with NHL.

The study showed across all four cycles that, for the overall and acute phases, 76.7% and 81.7% of patients, respectively, were complete responders (Table II), increasing to 90.5% of patients in the delayed phase. Palonosetron was shown to control both acute and delayed nausea. For the overall phase, patients reported no nausea (< 5 mm) in 68.8% of all cycles, with a corresponding CP rate of 72.2%. An emesis-free rate of 90.5% was recorded for the overall phase across all cycles, while rescue medication was not required in 81.7% of cycles. For all cycles the QoL assessment scores for nausea and vomiting, including FLIE, indicated a good ability of the patients to maintain the activities of daily life.

This is particularly noteworthy as the study chemotherapy regimen, CHOP (or R-CHOP), is now classified in the American Society of Clinical Oncology (ASCO) [21] and National Comprehensive Cancer Network (NCCN) [25] guidelines as highly emetogenic, and not moderately emetogenic, as at the time the present study was initiated. The current recommendations from ASCO, the Multinational Association of Supportive Care in Cancer and NCCN for treating CINV from highly emetogenic agents are for a three-drug combination of the NK_1 receptor antagonist aprepitant, a 5-HT_3 RA and dexamethasone [21,22]. The results of the present study suggest that the very high rate of control of emesis by palonosetron alone, recorded in the overall phase across all study cycles, may allow us to consider that the addition of aprepitant may be omitted.

The safety of palonosetron has previously been demonstrated in a number of phase III studies, including specific studies of the effect of palonosetron on QT elongation [4,5,8,26,27]. The present study supported these findings. Thus, the efficacy of single iv doses of 0.25 mg palonosetron in the control of CINV during MEC treatment previously reported for a single cycle in this clinical setting [20] has been confirmed for up to four repeated and consecutive cycles of MEC in the absence of any safety concerns. This also confirms, in hematological patients, the maintenance of the antiemetic efficacy of palonosetron over several cycles that has been reported in other clinical settings [10,17].

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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