



Real-world efficacy: intravenous palonosetron three-drug regimen for chemotherapy-induced nausea and vomiting with highly emetogenic chemotherapy

Lee S Schwartzberg^{*1}, Trent McLaughlin², Robert B Geller³, Nashat Y Gabrail⁴ & Stanley M Marks⁵

¹Division of Hematology/Oncology, Department of Medicine, University of Tennessee Health Sciences Center and West Cancer Center, 7945 Wolf River Blvd, Germantown, TN 38138, USA

²Real-World Evidence, Xcenda LLC, 4114 Woodlands Parkway, Suite 402, Palm Harbor, FL 34685, USA

³Medical Affairs, Heron Therapeutics, Inc., 4242 Campus Point Court, Suite 200, San Diego, CA 92121, USA

⁴Department of Oncology, Gabrail Cancer Center, 4875 Higbee Ave NW, Canton, OH 44718, USA

⁵Division of Medical Hematology/Oncology, UPMC Hillman Cancer Center, 5150 Centre Ave, 5th Floor Cancer Pavilion, Pittsburgh, PA 15232, USA

*Author for correspondence: Tel.: +1 901 683 0055; Fax: +1 901 685 2969; lschwartzberg@WESTCLINIC.com

Aim: Real-world palonosetron effectiveness was evaluated in an antiemetic regimen with highly emetogenic chemotherapy (HEC). **Patients & methods:** In this Phase IV, prospective, multicenter observational study, HEC-treated cancer patients received palonosetron, a neurokinin 1 receptor antagonist, and dexamethasone. Primary objective was to assess complete response (CR) for acute (≤ 24 h), delayed and overall (≤ 120 h) chemotherapy-induced nausea and vomiting. **Results:** Of 159 patients, 65.4% had breast cancer, 64.8% received anthracycline (doxorubicin)-plus-cyclophosphamide-containing chemotherapy; 155 completed one HEC cycle. CR was 60.0% acute, 39.4% delayed and 34.8% overall, and then increased (all phases) in 69 patients completing four HEC cycles. Anthracycline (doxorubicin) plus cyclophosphamide-receiving patients had especially low CR. **Conclusion:** Even within a recommended three-drug antiemetic regimen, palonosetron may provide suboptimal chemotherapy-induced nausea and vomiting control with HEC in real-world settings.

First draft submitted: 5 September 2018; Accepted for publication: 24 September 2018; Published online: 11 October 2018

Keywords: chemotherapy-induced nausea and vomiting • granisetron • palonosetron

Poorly controlled chemotherapy-induced nausea and vomiting (CINV) may impair quality-of-life of patients with cancer and lead to chemotherapy dose delays, reductions, or even discontinuations [1–4]. For patients receiving highly emetogenic chemotherapy (HEC), guidelines from the National Comprehensive Cancer Network (NCCN), American Society of Clinical Oncology (ASCO) and Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology recommend a three-drug prophylactic antiemetic regimen of a 5-hydroxytryptamine type 3 (5-HT₃) receptor antagonist (RA), dexamethasone, and a neurokinin 1 (NK-1) RA or a four-drug prophylactic antiemetic regimen with added olanzapine [5–9].

Available 5-HT₃ RAs include the first-generation agents granisetron, ondansetron and dolasetron, and the second-generation agent palonosetron, which has a longer half-life (approximately 40 h [10]) than oral and intravenous (iv.) first-generation 5-HT₃ RAs [11]. Two extended-release granisetron formulations are also available [12,13]. Intravenous palonosetron is indicated for preventing acute and delayed CINV in patients receiving moderately emetogenic chemotherapy (MEC) and acute CINV in patients receiving HEC [10]. Current NCCN, Multinational Association of Supportive Care in Cancer and European Society of Medical Oncology and ASCO guidelines recommend iv.

palonosetron as one option, in patients receiving HEC, for CINV prevention within three- and four-drug regimens of a 5-HT₃ RA, an NK-1 RA, dexamethasone and olanzapine [5–9,14].

Despite effective antiemetics and comprehensive guidelines, CINV control in patients receiving HEC is suboptimal, especially in the delayed phase [15–18], and nausea is often poorly controlled [19,20]. In a prospective study of CINV prevalence in patients with cancer undergoing their first chemotherapy cycle (HEC or MEC), 61.2% of patients reported some form of CINV; 58.4% reported delayed CINV (>24 h after chemotherapy administration, lasting several days) and 34.3% reported acute CINV (≤ 24 h after chemotherapy administration). Nausea occurred in 60.7% of patients and vomiting in 16.9%, highlighting the need for better nausea control. The most frequently prescribed antiemetic regimen included the 5-HT₃ RA palonosetron, the NK-1 RA aprepitant and the corticosteroid dexamethasone. However, fewer patients reported taking their antiemetic medications than were prescribed such medications [2]. In an observational study, even with prophylactic antiemetic treatment (three- or two-drug regimens) in compliance with 1999 ASCO guidelines for acute (89.2% regimens) and delayed (49.2% regimens) CINV [21], CINV occurred in 64.4% of chemotherapy cycles; 60.7% of patients experienced delayed CINV and 32.8% had acute CINV. Nausea was approximately 2.5-times more prevalent than vomiting across acute and delayed phases [22].

Consequently, it is important to understand the extent of the CINV problem in the real-world setting and to determine the degree of CINV control achieved in clinical practice. Also, palonosetron has been studied primarily in combination with dexamethasone, but without an NK-1 RA, so limited data are available for assessing the effectiveness of palonosetron in a three-drug regimen that includes an NK-1 RA. Therefore, this study was conducted to evaluate the real-world effectiveness of palonosetron, the preferred 5-HT₃ RA at the time of this study, as part of an ASCO guideline-recommended three-drug regimen with an NK-1 RA and dexamethasone [14], in patients receiving HEC.

Patients & methods

Study design & treatments

This Phase IV, prospective, multicenter, real-world observational study was conducted at seven US community practices, in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. The study was approved by the institutional review board for each participating site. Written informed consent was obtained for each patient.

Patients received standard of care as determined by their primary medical oncologist. All patients received palonosetron, an NK-1 RA (aprepitant or fosaprepitant), and dexamethasone, as well as the appropriate chemotherapy regimen. Antiemetic dosages were dispensed as directed by the treating physician. Rescue medications (all commercially available) were prescribed at physician's discretion and available to all patients. Data were collected only for patients who were prescribed iv. palonosetron.

Objectives

The primary objective was to assess complete response (CR) rate (i.e., no emetic episodes and no use of rescue medications) associated with iv. palonosetron, an NK-1 RA (aprepitant or fosaprepitant) and dexamethasone in patients receiving HEC. CRs were characterized for all completed chemotherapy cycles and for acute (0–24 h after chemotherapy), delayed (>24–120 h) and overall (0–120 h) CINV phases. CR rates were calculated for four cohorts: all patients who completed at least one HEC cycle; all who were scheduled for and completed four HEC cycles; by cancer type, all who completed at least one HEC cycle; and by chemotherapy regimen, all who completed at least one HEC cycle.

Secondary objectives included evaluation of the number and severity of patient-reported episodes of nausea, vomiting and retching associated with chemotherapy; use of rescue medication; and patient-reported satisfaction with their antiemetic regimen.

Patients

Eligible patients were men or women aged ≥18 years who had histologically or cytologically confirmed malignant disease, may have received prior chemotherapy, were entering cycle 1 of their current chemotherapy regimen, had Eastern Cooperative Oncology Group performance status (ECOG PS) 0–3, and had adequate bone marrow, liver and kidney function. Patients must have been scheduled for at least one, but no more than four, single-day HEC cycles with ≥7 days between cycles. Chemotherapy was defined as HEC by ASCO criteria [14] as follows: iv. carmus-

tine, iv. cisplatin ≥ 50 mg/m²; cyclophosphamide ≥ 1500 mg/m²; or dacarbazine, dactinomycin, mechlorethamine, streptozotocin or anthracycline plus cyclophosphamide (AC); in this study, the AC chemotherapies included doxorubicin as the anthracycline. Eligible patients were scheduled for a prophylactic antiemetic regimen including iv. palonosetron, an NK-1 RA (e.g., aprepitant, fosaprepitant) and dexamethasone, with dexamethasone also prescribed for days 2–4 following chemotherapy, consistent with NCCN antiemetic guidelines [5].

Patients were excluded if they were scheduled to receive any other chemotherapeutic agent from days 2 through 6 of any treatment cycles or had taken any 5-HT₃ RAs, phenothiazines, benzamides, domperidone, cannabinoids or NK-1 RAs within 5 days before chemotherapy initiation. Patients were also excluded if they had taken any benzodiazepine within 24 h before chemotherapy initiation or planned to take benzodiazepine during the study, unless they were receiving stable doses for ≥ 30 days before the study and were to continue the same dose throughout the study. Any patients who had corticosteroids or sedative antihistamines within 7 days before chemotherapy initiation, except as premedication for chemotherapy (e.g., taxanes, pemetrexed), were also excluded.

Assessments

Patients completed a daily diary during the first 5 days of each HEC cycle, recording the number of nausea, retching and emetic episodes, and their severity (1 = mild, 2 = moderate or 3 = severe). Patients unable to complete the diary for a given day were contacted by a study coordinator to collect diary data. Additionally, patients recorded information on their rescue medication use (on days 1 through 6) and satisfaction with antiemetic therapy (on day 5). Patients who completed a paper versus electronic diary were contacted via telephone by a study coordinator daily for each of days 1 through 6 to collect and transcribe data into the electronic diary.

Other assessments included physical examination and ECOG PS, typically performed at the day-1 visit of HEC cycle 1 or within 30 days before HEC cycle 1. Physical examinations were also performed and ECOG PS reported for HEC cycles 2 through 4, if applicable. Vital signs were assessed on day 1 of HEC cycle 1. Clinical laboratory assessments and electrocardiograms were recorded, if included in the patient's medical records.

Safety

Safety was not assessed in this study, but serious medical events (SMEs), defined as any unfavorable reaction or illness experienced by the patient that required medical intervention via an emergency room visit or hospitalization, were captured.

Statistical methods

A planned sample size of 160 evaluable patients would provide 20% oversampling, provide sufficient precision (have a sufficient sample size to observe enough events to calculate CR and compare with other published estimates), and minimize the effect of dropouts or missing information. The study protocol was amended to allow enrollment of 160 patients, with a minimum of 40 patients receiving four HEC cycles and the remaining 120 being followed for only one HEC cycle. Inclusion criteria were also amended to require that all patients must be scheduled to receive at least one, but no more than four, single-day HEC cycles, and antiemetic prophylaxis must follow NCCN guidelines. Eligibility criteria were modified to include patients scheduled to receive chemotherapy on days 1, 8 and 15, but not those who had 5-HT₃ RAs, phenothiazines, benzamides, domperidone, cannabinoids or NK-1 RAs within 5 days before chemotherapy initiation.

Analysis of the number of nausea, retching and emetic episodes during acute, delayed and overall CINV phases was conducted for four subgroups: all patients who completed one cycle of HEC; all who were scheduled for and completed four cycles of HEC; all, by cancer type, who completed at least one cycle of HEC; and all, by chemotherapy regimen, who completed at least one cycle of HEC. The number of episodes for the overall phase was calculated by adding the number of episodes in acute and delayed phases.

All statistical analyses were performed using SAS[®] Version 9.3 or higher. Continuous variables were assessed using descriptive statistics. Frequencies and percentages were used for discrete and categorical variables. No imputations were performed on missing data, and patients who dropped out of the study were not replaced.

Results

Patients

During the study period (June 2015–March 2016), 168 patients were screened across seven clinical sites within the USA and 161 were enrolled. Of enrolled patients, two were ineligible; one received lorazepam premedication, and

Table 1. Patient demographics and baseline clinical characteristics.

Characteristics	Overall population, N = 159
Age, mean (SD)	56.4 (10.9)
Women, n (%)	123 (77.4)
White, non-Hispanic, n (%)	123 (77.4)
ECOG PS, n (%)	
– 0	117 (74.0)
– 1	39 (24.5)
– 2	2 (1.3)
Most common cancer diagnosis in >1% of patients, n (%)	
– Breast	104 (65.4)
– Lung	24 (15.1)
– Hodgkin's lymphoma	9 (5.7)
– Bladder cancer	5 (3.1)
– Head and neck cancer	4 (2.5)
– Urothelial cancer	4 (2.5)
– Mouth cancer	2 (1.3)
Cancer stage, n (%)	
– I	21 (13.2)
– II	81 (50.9)
– III	34 (21.5)
– IV	19 (11.9)
– Unknown	6 (3.8)
Chemotherapy regimens, n (%)	
– Doxorubicin + cyclophosphamide	103 (64.8)
– Cisplatin	45 (28.3)
– Dacarbazine	9 (5.7)
– Doxorubicin + cyclophosphamide + cisplatin	2 (1.3)
ECOG PS: Eastern Cooperative Oncology Group performance status; n: Subset of the total population for characteristics/category listed; N: Total population; SD: Standard deviation.	

another received granisetron, rather than palonosetron, as part of the triple antiemetic regimen. The 159 eligible enrolled patients had a mean age of 56.4 years, 123 (77.4%) were women and 123 (77.4%) were non-Hispanic white. Most had a breast cancer diagnosis (65.4%), and the majority (74.0%) had baseline ECOG PS of 0 (Table 1). The most common chemotherapy regimen administered was doxorubicin plus cyclophosphamide (an AC) in 103 patients (64.8%). Four patients lacked sufficient data for analysis, so data were analyzed from 155 patients who completed at least one HEC cycle (Figure 1). 22 patients terminated from the study before their expected end date, the most common reason being patient consent withdrawal (n = 5, 3.1%).

Efficacy

Of the 155 patients who completed one HEC cycle, 93 (60.0%) achieved a CR in the acute phase and 61 (39.4%) in the delayed phase (Table 2). Furthermore, a subset of 69 patients was followed for up to four HEC cycles (Table 3).

Analysis by cancer type for all patients who completed at least one cycle of HEC showed that of 103 patients with breast cancer, 56 (54.4%) and 41 (39.8%) had a CR in the acute and delayed phases, respectively. For 24 patients with lung cancer, 19 (79.2%) and 11 (45.8%) had a CR in the acute and delayed phases, respectively (Table 2). CRs for patients with other cancer types are also shown in Table 2.

Analysis by chemotherapy regimen for all patients who completed at least one cycle of HEC showed that CR rates were highest in the 43 patients receiving cisplatin, with CRs in 31 patients (72.1%) in the acute phase and 18 patients (41.9%) in the delayed phase. In the 102 patients receiving doxorubicin plus cyclophosphamide, CRs occurred in 55 patients (54.0%) in the acute phase and 41 patients (40.2%) in the delayed phase (Table 2).

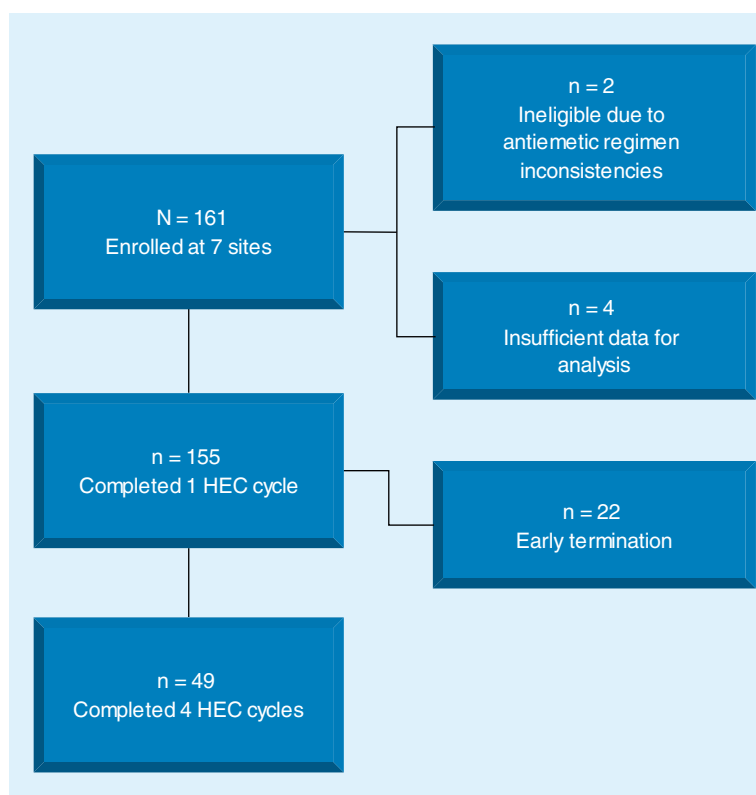


Figure 1. Patient disposition.
HEC: Highly emetogenic chemotherapy; n: Subset of the total population for characteristics/category listed; N: Total population.

Table 2. Complete response rates, by cancer type and chemotherapy regimen, for patients who completed at least one highly emetogenic chemotherapy treatment cycle.

	Acute-phase CR (0–24 h) n (%)	Delayed-phase CR (24–120 h) n (%)	Overall-phase CR (0–120 h) n (%)
Complete response after one cycle of HEC (N = 155)	93 (60.0)	61 (39.4)	54 (34.8)
Cancer type			
Breast cancer (n = 103)	56 (54.4)	41 (39.8)	35 (34.0)
Lung cancer (n = 24)	19 (79.2)	11 (45.8)	11 (45.8)
Hodgkin's lymphoma (n = 8)	5 (62.5)	2 (25.0)	1 (12.5)
Bladder cancer (n = 5)	3 (60.0)	2 (40.0)	2 (40.0)
Head and neck cancer (n = 4)	3 (75.0)	1 (25.0)	1 (25.0)
Urothelial cancer (n = 4)	2 (50.0)	1 (25.0)	1 (25.0)
Chemotherapy regimen			
Doxorubicin + cyclophosphamide (n = 102)	55 (54.0)	41 (40.2)	35 (34.3)
Cisplatin (n = 43)	31 (72.1)	18 (41.9)	18 (41.9)
Dacarbazine (n = 8)	5 (62.5)	2 (25.0)	1 (12.5)
Doxorubicin + cyclophosphamide + cisplatin (n = 2)	2 (100.0)	0 (0.0)	0 (0.0)

CR: Complete response; HEC: Highly emetogenic chemotherapy; n: Subset of the total population for characteristics/category listed; N: Total population.

Among the 69 patients followed up to four HEC cycles, CR rates improved during subsequent cycles in the acute and delayed phases; CR rates in the acute phase ranged from 56.5 to 71.4%, and in the delayed phase from 33.3 to 61.2% (Table 3).

Patient-reported evaluation of the number and severity of nausea, retching and emetic episodes for patients who completed at least one HEC cycle is shown in Table 4. The number and severity of nausea episodes were notable. In the total population of 155 patients, 166 nausea episodes occurred in the acute phase and 603 in the delayed

Table 3. Complete response rates for patients who completed four highly emetogenic chemotherapy treatment cycles.

HEC treatment cycle	Acute-phase CR (0–24 h) n (%)	Delayed-phase CR (>24–120 h) n (%)	Overall-phase CR (0–120 h) n (%)
HEC cycle 1 (n = 69)	39 (56.5)	23 (33.3)	20 (29.0)
HEC cycle 2 (n = 58)	39 (67.2)	29 (50.0)	28 (48.3)
HEC cycle 3 (n = 55)	37 (67.3)	30 (54.6)	27 (49.1)
HEC cycle 4 (n = 49)	35 (71.4)	30 (61.2)	30 (61.2)

CR: Complete response; HEC: Highly emetogenic chemotherapy; n: Subset of the total population for characteristics/category listed.

Table 4. Nausea, retching and emetic episodes for patients who completed at least one highly emetogenic chemotherapy treatment cycle.

Episode	Acute phase (0–24 h) N = 155	Delayed phase (>24–120 h) N = 155	Overall phase (0–120 h) N = 155
Nausea episodes			
– Total number, N	166	603	769
– Severity, mean (SD)	1.57 (0.70)	1.47 (0.64)	1.49 (0.65)
Retching episodes			
– Total number, N	32	96	128
– Severity, mean (SD)	1.75 (0.62)	1.45 (0.55)	1.52 (0.57)
Emetic episodes			
– Total number, N	7	45	52
– Severity, mean (SD)	0.05 (0.31)	1.53 (0.61)	1.48 (0.59)

HEC: Highly emetogenic chemotherapy; SD: Standard deviation; N: Total population.

phase; the mean severity of these episodes was mild to moderate (1.57 and 1.47, respectively, during acute and delayed phases) (Table 4).

Among patients who completed at least one HEC cycle, 100 patients utilized rescue medication; the most commonly used was prochlorperazine (173 uses), followed by ondansetron (116 uses) and lorazepam (75 uses). Other rescue medications included promethazine (11 uses), metoclopramide, hyoscine hydrobromide and alprazolam (one use each).

Overall patient satisfaction with antiemetic therapy was analyzed for all patients who completed at least one HEC cycle. Overall, 96 patients (62.0%) were ‘very satisfied’ and 48 (31.0%) were ‘satisfied’ with their antiemetic therapy.

Safety

Although safety was not a primary or secondary study end point, SMEs were reported for eight patients at four sites. Six of these patients were hospitalized for 3–18 days for a variety of diagnoses; only one experienced a CINV-related SME. The other two patients had SMEs not related to CINV and emergency room visits lasting 2 and 24 h.

Discussion

In this real-world study of palonosetron used within a three-drug antiemetic regimen in patients receiving single-day HEC, 60% achieved CR in the acute phase, and 39% in the delayed phase in cycle 1. For patients who completed four HEC cycles, CR rates varied from 56 to 72% in the acute phase, and 33 to 61% in the delayed phase. Interestingly, even though a substantial proportion of patients did not achieve CR in the acute and delayed CINV phases, 93% were at least satisfied with their antiemetic treatment and 62% were very satisfied. This may reflect patients’ low expectation for CINV control and their assumption that they will experience nausea and vomiting. In patients receiving AC chemotherapy (commonly administered to women with breast cancer), CR rates have been shown to be especially low: 54% in the acute phase, 40% in the delayed phase and 34% in the overall phase [23–25]. Additionally, while CR rates increased over each chemotherapy cycle in patients who received up to four HEC cycles, patient numbers decreased over successive cycles. This may be due to patients discontinuing the study for various reasons, including noncompliance with prescribed medication or protocol requirement, additional HEC

treatment not being recommended, modification of the antiemetic regimen to one that no longer followed ASCO guideline recommendations, or switching to a different antiemetic regimen, so patients who responded well to the palonosetron regimen continued to receive treatment.

Palonosetron is a widely used 5-HT₃ RA, perhaps because of its extended half-life compared with first-generation oral and iv. 5-HT₃ RAs, but the approved indication for iv. palonosetron following HEC is to prevent acute CINV only [10], and the results of this real-world study do not reflect CR rates in clinical trials [10,13,26,27]. In a pivotal Phase III trial, single-dose iv. palonosetron 0.25 mg was noninferior to iv. ondansetron 32 mg (a guideline-recommended 5-HT₃ RA [9]) in controlling acute CINV following HEC in the absence of an NK-1 RA (a nonstandard antiemetic regimen) [5–9,28].

Recently, a double-blind, randomized Japanese study, reported as an abstract, compared two three-drug antiemetic regimens, containing palonosetron or granisetron combined with an NK-1 RA and dexamethasone, in patients receiving AC-based HEC. No significant difference was observed between study arms in delayed phase CR, even though palonosetron was administered at 0.75 mg, three-times the recommended dose in the USA [29]. Additionally, in another randomized, double-blind Japanese study (reported as an abstract) in 341 patients with breast cancer who received AC-based chemotherapy, palonosetron 0.75 mg failed to show superiority over granisetron 1 mg in controlling delayed CINV when each drug was combined with fosaprepitant and dexamethasone [30]. The most recent NCCN guidelines no longer prefer iv. palonosetron over other 5-HT₃ RAs in the HEC setting when given with an NK-1 receptor antagonist [5].

Overall, in some of these clinical trials of palonosetron, approximately half of patients, especially patients with breast cancer receiving AC chemotherapy, still experienced delayed phase CINV [29,30]. Consistent with these findings, our real-world observational study results indicate that CINV prevention with palonosetron in a three-drug antiemetic regimen was not optimal, especially in the delayed phase, and that nausea, particularly, was not well controlled, per patient report. Thus, improved CINV control in patients receiving HEC remains an unmet medical need.

In a randomized, double-blind Phase III trial of a three-drug antiemetic regimen with or without olanzapine in patients receiving HEC, nausea control in cycle 1 was significantly greater with olanzapine added to the three-drug regimen in the acute, delayed and overall phases of CINV. Similarly, CR rates in cycle 1 were significantly higher with the four-drug regimen than with the three-drug regimen in the acute (86 vs 65%), delayed (67 vs 52%) and overall (64 vs 41%) phases, respectively [19]. CR rates for the three-drug regimen in that trial were somewhat higher during each phase than in the current real-world study, but are consistent in that CR rates were higher in the acute than delayed phase of CINV. The higher CR rates with the olanzapine-containing regimen suggest that this four-drug regimen may be another option for CINV prevention in patients receiving HEC, for whom it is now a recommended option as per NCCN antiemetic guidelines [5].

Another option that may improve CINV prevention, especially in the delayed phase, is the use of extended-release formulations of antiemetics within a guideline-recommended regimen. Granisetron is the only first-generation 5-HT₃ RA available in extended-release formulations, a granisetron transdermal delivery system (a patient-administered patch) and a granisetron extended-release subcutaneous injection (GERSC, administered by a healthcare professional) [12,13]. In one study of GERSC in patients receiving MEC or HEC, 48% of MEC-receiving patients and 40% of HEC-receiving patients failed to achieve CR with palonosetron in cycle 1; 37% of these patients were then given GERSC in cycle 2. Greater than 50% of those who failed palonosetron in cycle 1 achieved CR with GERSC in cycle 2 in the acute phase; CR rates were slightly less in the delayed phase. These findings indicate that failure of palonosetron may not extend to GERSC [31].

Additional options include the use of netupitant (oral)/fosnetupitant (iv.) and palonosetron (NEPA) fixed combination drug combined with dexamethasone for CINV prevention in acute and delayed phases. However, the iv. formulation of netupitant (oral)/fosnetupitant (iv.) and palonosetron has not been studied in patients receiving AC-based chemotherapy [32].

In an observational real-world study, it is not always possible to attribute observed findings to the prescribed antiemetic regimen rather than to other possible causes. Furthermore, the number of CINV episodes, their severity and the use of rescue medications were recorded by the patients, so are subjective in nature. However, observational studies more accurately reflect a therapy's performance in clinical practice, encompassing a wide range of patients within different clinical settings, compared with the strict requirements of randomized controlled clinical trials.

Conclusion

This real-world observational study indicates that patients receiving HEC may be experiencing suboptimal CINV control even when using a guideline-recommended three-drug antiemetic regimen that includes palonosetron; alternative regimens should be explored.

Summary points

What is already known about this subject?

- Control of chemotherapy-induced nausea and vomiting in patients receiving highly emetogenic chemotherapy (HEC), especially in the delayed phase, remains suboptimal.
- It is important to understand the real-world effectiveness of palonosetron within a three-drug antiemetic regimen that includes a neurokinin 1 receptor antagonist in patients receiving HEC.

What are the new findings?

- Within single-day HEC-receiving patients treated with palonosetron, 60% achieved complete response (CR) in the acute phase, and 39% achieved CR in the delayed phase.
- Within patients receiving four HEC cycles, CR rates varied from 56 to 72% in the acute phase and 33 to 61% in the delayed phase.
- These real-world studies with palonosetron do not reflect CR rates in the palonosetron clinical trials.

Impact on clinical practice

- Other 5-hydroxytryptamine type 3 RAs such as the granisetron extended-release formulation may provide improved chemotherapy-induced nausea and vomiting control, especially in the delayed phase.

Financial & competing interests disclosure

Research support was provided by Heron Therapeutics, Inc. (San Diego, CA, USA). LS Schwartzberg has had a consultant or advisory role with Helsinn, Heron, Merck and Tesaro and received research funding from Helsinn. T McLaughlin has been employed by and received research funding from Xcenda LLC. RB Geller has been employed by Heron and has stock or other ownership with Amgen, Gilead and Heron. NY Gabrail has received honoraria from AbbVie, Heron, J&J, Mateon and Taiho; has had consultant or advisory role with AbbVie, Bayer, Heron, J&J and Taiho; has been on speaker's bureaus for Heron, J&J and Taiho; and has received research funding from AbbVie, Acerta, Amgen, Bayer, BMS, Celgene, Gilead, Halozyme, Incyte, J&J, Sanofi and Taiho. SM Marks has had stock or other ownership with Amgen, BMS and Merck and received honoraria from Integra Connect. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by N Parikh, of SciStrategy Communications, Conshohocken, PA, USA, and funded by Heron Therapeutics, Inc., San Diego, CA, USA. Data analysis support was provided by K McLeod and A Quillen, of Xcenda LLC.

Ethical conduct of research

This real-world observational study was conducted at seven US community practices, in accordance with the International Conference on Harmonisation Guideline for Good Clinical Practice and the Declaration of Helsinki. The study was approved by the institutional review board for each participating site. Written informed consent was obtained for each patient.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. Bloechl-Daum B, Deuson RR, Mavros P, Hansen M, Herrstedt J. Delayed nausea and vomiting continue to reduce patients' quality of life after highly and moderately emetogenic chemotherapy despite antiemetic treatment. *J. Clin. Oncol.* 24(27), 4472–4478 (2006).
2. Haiderali A, Menditto L, Good M, Teitelbaum A, Wegner J. Impact on daily functioning and indirect/direct costs associated with chemotherapy-induced nausea and vomiting (CINV) in a US population. *Support. Care Cancer* 19(6), 843–851 (2011).
3. Van Laar ES, Desai JM, Jatoti A. Professional educational needs for chemotherapy-induced nausea and vomiting (CINV): multinational survey results from 2388 health care providers. *Support. Care Cancer* 23(1), 151–157 (2015).
4. Sommariva S, Pongiglione B, Tarricone R. Impact of chemotherapy-induced nausea and vomiting on health-related quality of life and resource utilization: a systematic review. *Crit. Rev. Oncol. Hematol.* 99, 13–36 (2016).

- **Comprehensive review outlining evidence of the effect of chemotherapy-induced nausea and vomiting (CINV) on patient's quality of life and its healthcare cost burden.**
- 5. NCCN. NCCN clinical practice guidelines in oncology: antiemesis – v3.2018. (2018). www.nccn.org/professionals/physician_gls/default.aspx
- **US clinical practice guidelines for the prevention and treatment of CINV.**
- 6. Roila F, Molassiotis A, Herrstedt J *et al.* 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. *Ann. Oncol.* 27(Suppl. 5), v119–v133 (2016).
- **European clinical practice guidelines for the prevention and treatment of nausea and vomiting induced by moderately emetogenic chemotherapy.**
- 7. Aapro M, Gralla R, Herrstedt J, Molassiotis A, Roila F. MASCC/ESMO antiemetic guideline 2016. (2016). www.mascc.org/antiemetic-guidelines
- 8. Herrstedt J, Roila F, Warr D *et al.* 2016 Updated MASCC/ESMO consensus recommendations: prevention of nausea and vomiting following high emetic risk chemotherapy. *Support. Care Cancer* 25(1), 277–288 (2017).
- **European clinical practice guidelines for the prevention and treatment of nausea and vomiting induced by highly emetogenic chemotherapy.**
- 9. Hesketh PJ, Kris MG, Basch E *et al.* Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* 35(28), 3240–3261 (2017).
- **US clinical practice guidelines for the prevention and treatment of CINV.**
- 10. Aloxi (palonosetron HCl) injection for intravenous use, prescribing information. Eisai, Inc., NJ, USA (2015).
- 11. Botrel TE, Clark OA, Clark L, Paladini L, Faleiros E, Pegoretti B. Efficacy of palonosetron (PAL) compared to other serotonin inhibitors (5-HT₃R) in preventing chemotherapy-induced nausea and vomiting (CINV) in patients receiving moderately or highly emetogenic (MoHE) treatment: systematic review and meta-analysis. *Support. Care Cancer* 19(6), 823–832 (2011).
- 12. Sancuso (granisetron transdermal system), prescribing information. ProStrakan, Inc., NJ, USA (2017).
- 13. Sustol (granisetron) extended-release injection, for subcutaneous use, prescribing information. Heron Therapeutics, CA, USA (2017).
- 14. Basch E, Prestrud AA, Hesketh PJ *et al.* Antiemetics: American Society of Clinical Oncology clinical practice guideline update. *J. Clin. Oncol.* 29(31), 4189–4198 (2011).
- 15. Hilarius DL, Kloeg PH, van der Wall E, van den Heuvel JJ, Gundy CM, Aaronson NK. Chemotherapy-induced nausea and vomiting in daily clinical practice: a community hospital-based study. *Support. Care Cancer* 20(1), 107–117 (2012).
- 16. Geling O, Eichler HG. Should 5-hydroxytryptamine-3 receptor antagonists be administered beyond 24 hours after chemotherapy to prevent delayed emesis? Systematic re-evaluation of clinical evidence and drug cost implications. *J. Clin. Oncol.* 23(6), 1289–1294 (2005).
- 17. Aapro M, Molassiotis A, Dicato M *et al.* The effect of guideline-consistent antiemetic therapy on chemotherapy-induced nausea and vomiting (CINV): the Pan European Emesis Registry (PEER). *Ann. Oncol.* 23(8), 1986–1992 (2012).
- 18. Schnadig ID, Agajanian R, Dakhil C *et al.* APF530 (granisetron injection extended-release) in a three-drug regimen for delayed CINV in highly emetogenic chemotherapy. *Future Oncol.* 12(12), 1469–1481 (2016).
- **Phase III trial of granisetron extended-release subcutaneous versus ondansetron, each in a three-drug regimen, for the prevention of delayed CINV in patients receiving highly emetogenic chemotherapy.**
- 19. Navari RM, Qin R, Ruddy KJ *et al.* Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. *N. Engl. J. Med.* 375(2), 134–142 (2016).
- 20. Ng TL, Hutton B, Clemons M. Chemotherapy-induced nausea and vomiting: time for more emphasis on nausea? *Oncologist* 20(6), 576–583 (2015).
- 21. Gralla RJ, Osoba D, Kris MG *et al.* Recommendations for the use of antiemetics: evidence-based, clinical practice guidelines. American Society of Clinical Oncology. *J. Clin. Oncol.* 17(9), 2971–2994 (1999).
- 22. Ihbe-Heffinger A, Ehlken B, Bernard R *et al.* The impact of delayed chemotherapy-induced nausea and vomiting on patients, health resource utilization and costs in German cancer centers. *Ann. Oncol.* 15(3), 526–536 (2004).
- 23. Schwartzberg LS, Modiano MR, Rapoport BL *et al.* Safety and efficacy of rolapitant for prevention of chemotherapy-induced nausea and vomiting after administration of moderately emetogenic chemotherapy or anthracycline and cyclophosphamide regimens in patients with cancer: a randomised, active-controlled, double-blind, Phase III trial. *Lancet Oncol.* 16(9), 1071–1078 (2015).
- 24. Schnadig ID, Agajanian R, Dakhil C *et al.* APF530 versus ondansetron, each in a guideline-recommended three-drug regimen, for the prevention of chemotherapy-induced nausea and vomiting due to anthracycline plus cyclophosphamide-based highly emetogenic chemotherapy regimens: a *post hoc* subgroup analysis of the Phase III randomized MAGIC trial. *Cancer Manag. Res.* 9, 179–187 (2017).

25. Hutton B, Clemons M, Mazzarello S, Kuchuk I, Skidmore B, Ng T. Identifying an optimal antiemetic regimen for patients receiving anthracycline and cyclophosphamide-based chemotherapy for breast cancer – an inspection of the evidence base informing clinical decision-making. *Cancer Treat. Rev.* 41(10), 951–959 (2015).
26. Kolesar JM, Eickhoff J, Vermeulen LC. Serotonin type 3-receptor antagonists for chemotherapy-induced nausea and vomiting: therapeutically equivalent or meaningfully different? *Am. J. Health Syst. Pharm.* 71(6), 507–510 (2014).
27. Yeh YC, Blouin GC, Reddy P. Evidence to support use of palonosetron over generic serotonin type 3-receptor antagonists for chemotherapy-induced nausea and vomiting. *Am. J. Health Syst. Pharm.* 71(6), 500–506 (2014).
28. Aapro MS, Grunberg SM, Manikhas GM *et al.* A Phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. *Ann. Oncol.* 17(9), 1441–1449 (2006).
29. Saito M, Uomori T, Miura K *et al.* Comparison between 1st and 2nd generation serotonin receptor antagonists in triplet antiemetic therapy in breast cancer patients – according to recent multi-institutional double-blind randomized study. *Support. Care Cancer* 25(Suppl. 2), S21–S266, Abstract PS054 (2017).
30. Matsumoto K, Takahashi M, Sato K *et al.* Palonosetron or granisetron for prevention of CINV in patients with breast cancer receiving dexamethasone and fosaprepitant following anthracycline plus cyclophosphamide (AC) regimen. *J. Clin. Oncol.* 33, Abstract 9598 (2015).
31. Arevalo-Araujo R, O’Boyle E, Cooper W, Robertson PA. Recovery of complete antiemetic response with APF530 during treatment with moderately (MEC) and highly (HEC) emetogenic chemotherapy regimens in patients who failed palonosetron. *J. Clin. Oncol.* 31(15 Suppl.), Abstract e20569 (2013).
32. Akynzeo (netupitant and palonosetron) capsules, (fosnetupitant and palonosetron) for injection, prescribing information. Helsinn Healthcare SA, Lugano, Switzerland (2018).