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ORIGINAL RESEARCH

The impact of 5-hydroxytryptamine-receptor antagonists on chemotherapy treatment adherence, treatment delay, and nausea and vomiting

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Purpose: To determine the incidence of chemotherapy-induced nausea/vomiting (CINV) and chemotherapy treatment delay and adherence among patients receiving palonosetron versus other 5-hydroxytryptamine receptor antagonist (5-HT_3 RA) antiemetics.

Materials and methods: This retrospective claims analysis included adults with primary malignancies who initiated treatment consisting of single-day intravenous highly emetogenic chemotherapy (HEC) or moderately EC (MEC) regimens. Treatment delay was defined as a gap in treatment at least twice the National Comprehensive Cancer Network-specified cycle length, specific to each chemotherapy regimen. Treatment adherence was determined by the percentage of patients who received the regimen-specific recommended number of chemotherapy cycles within the recommended time frame.

Results: We identified 1,832 palonosetron and 2,387 other 5-HT_3 RA ("other") patients who initiated HEC therapy, and 1,350 palonosetron users and 1,379 patients on other antiemetics who initiated MEC therapy. Fewer patients receiving palonosetron experienced CINV versus other (HEC, 27.5% versus 32.2%, P=0.0011; MEC, 36.1% versus 41.7%, P=0.0026), and fewer treatment delays occurred among patients receiving palonosetron versus other (HEC, 3.2% versus 6.0%, $P<0.0001$; MEC, 17.0% versus 26.8%, $P<0.0001$). Compared with the other cohort, patients receiving palonosetron were significantly more adherent to the index chemotherapy regimen with respect to the recommended time frame (HEC, 74.7% versus 69.7%, P=0.0004; MEC, 43.1% versus 37.3%, P=0.0019) and dosage (HEC, 27.3% versus 25.8%, P=0.0004; MEC, 15.0% versus 12.6%, P=0.0019).

Conclusion: Palonosetron more effectively reduced occurrence of CINV in patients receiving HEC or MEC compared with other agents in this real-world setting. Additionally, patients receiving palonosetron had better adherence and fewer treatment delays than patients receiving other 5-HT_3 RAs.

Keywords: palonosetron, adherence, CINV, delay of therapy, observational, health services research

Introduction

Nausea and vomiting are common chemotherapy-associated side effects ranked by patients as especially distressing.[1–7] Chemotherapy-induced nausea and vomiting (CINV) can cause psychological distress, nutritional deficiencies, and reduced quality of life among patients receiving chemotherapy.[5–8] Furthermore, its occurrence may potentially affect adherence to chemotherapy regimens, leading to treatment delays or receipt of fewer treatments or lower dosages than recommended.[9,10] Such

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events may have an adverse effect on treatment efficacy, ultimately resulting in suboptimal clinical outcomes and potentially increased health care-related resource utilization and costs.[3]

Recognizing the importance of preventing and managing CINV, leading oncology societies have issued treatment guidelines[11–13,29] recommending 5-hydroxytryptamine-receptor antagonists (5-HT_3 RAs) as the preferred medication class to effectively prevent CINV in patients receiving highly emetogenic chemotherapy (HEC) or moderately EC (MEC).[19,20] Compared to the older agents, palonosetron – a newer 5-HT_3 RA – is pharmacologically distinct, with a longer half-life and greater receptor-binding affinity, allosteric binding to serotonin receptors with positive cooperativity, and cross talk with Neurokinin-1 (NK-1) receptors.[21–23] While the early 5-HT_3 RA compounds were considered equally efficacious,[19] palonosetron demonstrated greater efficacy than active comparators in preventing CINV in patients receiving HEC or MEC in multiple clinical trials.[20,24–26] Hatoum et al compared palonosetron with other 5-HT_3 RAs in a real-world setting among patients with breast/lung cancer undergoing cisplatin/carboplatin treatments.[19,27] They concluded that patients who received prophylaxis with palonosetron had a significantly lower risk of CINV events than those who had received other 5-HT_3 RA agents. Furthermore, those breast/lung cancer patients receiving palonosetron experienced 49.5% and 29.1% fewer CINV days, respectively.[27] Their study focused on serious CINV events resulting in hospital or emergency department admissions, and did not include CINV events occurring in an outpatient context. Craver et al found that prophylactic administration of palonosetron among patients with hematologic malignancies who were receiving HEC/MEC resulted in a 20.4% decrease in CINV event rate per cycle compared with patients receiving other 5-HT_3 RAs.[28] However, while 5-HT_3 RA agents have been proven effective in preventing CINV, little is known regarding their impact on chemotherapy treatment adherence and delay. To address these questions, a real-world study was designed comparing patients who received palonosetron with those who received other 5-HT_3 RAs on incidence of acute and delayed CINV and chemotherapy treatment delay and adherence. This study also contributes to the development of methods to assess medication adherence for intravenous (IV) agents.

Materials and methods

This was an observational nested case–control study using data from the HealthCore Integrated Research Database (HIRD^{SM}). The HIRD is an integrated medical and pharmacy-claims and laboratory-result database of commercially insured patients from 14 major commercial health plans across the US representing approximately 45 million patient-lives dating as far back as January 1, 2001.

Cohort creation

The index date was defined as the earliest medical or pharmacy claim date for an IV HEC or MEC between January 1, 2002 and October 31, 2010. All patients included in the study were adults (≥18 years of age as of the index date) who had one or more medical claims with a diagnosis of primary malignant breast, lung, or colorectal neoplasm during the baseline period, which was defined as the 12 months before the index date. All patients had continuous medical and pharmacy health plan eligibility for at least 12 months pre- and 12 months postindex date. Patients were excluded if they 1) had a secondary malignant neoplasm or primary neoplasms at multiple sites, 2) had preindex HEC or MEC claims, 3) initiated multiday chemotherapy, 4) received oral chemotherapy alone or in combination with an IV formulation, 5) switched from a single-day-per-cycle chemotherapy regimen to multiday chemotherapy, or 6) had medical claim(s) for pregnancy, labor, or delivery in the 6 months postindex.

Lastly, in order to create clean comparison cohorts, patients receiving both palonosetron and any of the "other" 5-HT_3 RAs any time during the course of one or more chemotherapy treatment cycles were excluded from the analysis. The remaining patients were stratified into either the palonosetron or other 5-HT_3 RA treatment cohorts. Specifically, patients in the palonosetron group received only palonosetron and no other IV 5-HT_3 RA agent (ie, dolasetron, granisetron, and/or ondansetron; see Table S1) as prophylactic or rescue therapy beginning 1 day before through 5 days after the start of any chemotherapy treatment cycle; those in the other 5-HT_3 RA cohort were allowed to receive any prophylactic 5-HT_3 RA agent other than palonosetron.

Assignment of chemotherapy regimens

Index HEC and MEC agents were defined as any chemotherapeutic agent classified as having a known high or moderate emetogenic potential (Table S2).[29] Chemotherapy agents were identified using generic product identifier (GPI) and Healthcare Common Procedure Coding System (HCPCS) codes. Chemotherapy dose determined the HEC/MEC status of certain chemotherapy drugs (eg, cyclophosphamide and cisplatin) by calculating the index dose administered and then applying the National Comprehensive Cancer Network®

(NCCN®)-recommended Guidelines available at the time of the study for classification (Table S3).[29] Because only single-day administration regimens were included in the study, the average dose was equal to the average strength, as noted on medical or pharmacy claims. Body-surface area (BSA) was not available on claim forms, so published BSA estimates of cancer patients were used to determine the average dose per square meter.[30] The standard estimates used were 1.91 m^2 for men (95% confidence interval [CI] 1.90–1.92) and 1.71 m^2 for women (95% CI 1.70–1.72).

For regimens involving a combination of chemotherapeutic agents, the agent with the highest emetic risk defined the risk of the combination (ie, one MEC agent and one HEC agent equaled an HEC regimen; one lowly EC [LEC] and one MEC equaled an MEC regimen).[12,13] Two MEC agents were classified as HEC; however, two LEC agents remained a lowly emetogenic regimen (Table 1).[31] Additional information on the step-by-step regimen identification can be found in the Supplementary materials.

Claims for index chemotherapy agents dated 7 days or later after the beginning of the cycle were designated as the beginning of the subsequent cycle, and so on until the end of the 12-month observation period. The end of a chemotherapy cycle was determined using either the passing of the NCCN-recommended number of weeks between two cycles (Table 2), which was specific to each treatment regimen, or the start date of the subsequent treatment cycle, whichever occurred earlier.

Outcome measures

Acute CINV was identified by *International Classification of Diseases*, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes for nausea and vomiting, persistent vomiting, or volume depletion, or current procedural terminology codes for hydration, on the day of chemotherapy (Table S1). Delayed CINV was identified by the same ICD-9-CM and CPT codes for nausea and vomiting, volume depletion and hydration, as well as GPI/HCPCS codes for IV rescue medications (dexamethasone, fosaprepitant, diphenhydramine, promethazine, haloperidol, prochlorperazine, lorazepam, or metoclopramide) or 5-HT$_3$ RAs (Table S1) between the day after chemotherapy and day 5 of the chemotherapy cycle of interest. CINV events were assessed on a patient- and cycle-level basis.

Table 1 Algorithm to identify HEC and MEC regimens

Regimen makeup	HEC/MEC classification of regimen
Any HEC drug	HEC
Two or more MEC drugs	HEC
One MEC drug with or without low or minimal emetogenic chemotherapy (LEC)	MEC
Multiple LEC drugs	LEC

Abbreviations: HEC, highly emetogenic chemotherapy; MEC, moderately EC; LEC, lowly EC; EC, emetogenic chemotherapy.

Each index chemotherapy regimen was assigned a total number of chemotherapy cycles and an allowed gap between chemotherapy cycles according to the recommendations of the 2011 NCCN Clinical Practice Guidelines In Oncology (NCCN Guidelines®) (Table 2).[14–18] For example, a lung cancer patient on cisplatin (index dose of 100 mg/m^2) and vinorelbine would be assumed to have initiated a therapy involving four treatment cycles with an allowed rest period of 4 weeks between each cycle.

Treatment delay was measured in two ways: 1) the proportion of patients who delayed their index chemotherapy based on the presence of a significant gap between two chemotherapy cycles, and 2) the mean and median time from the index date to the date of treatment delay. Delay of therapy was defined as a gap in treatment exceeding twice the NCCN-specified cycle length specific to each chemotherapy regimen (Table 2). The date of treatment delay was the date of the last chemotherapy cycle start date prior to delay plus one cycle length. For patients on combination regimens, delay of any one agent involved in the regimen constituted delay of the entire regimen. We also performed a sensitivity analysis around the permissible treatment gap, assigning a lower limit of 1.5 times the NCCN-recommended cycle length and an upper limit of three times the NCCN-recommended cycle length.

Treatment adherence was measured in four related ways: the percentage of patients who received the 1) recommended number of cycles for their specific chemotherapy regimen, as determined by NCCN guidelines, 2) recommended number of chemotherapy cycles for their regimen within the recommended time frame, 3) recommended chemotherapy dose within a 10% margin, and 4) recommended number of cycles within the specified time frame at the expected dose. We used measure 2 as our primary measure of adherence. Patients on multiagent regimes were required to be adherent with each component of the regimen to be considered adherent overall.

Statistical analysis

Descriptive statistics were used to characterize the incidence of acute and delayed CINV, as well as baseline patient characteristics, such as primary cancer site and chemotherapy regimen. Means/standard deviations were used for

Table 2 Chemotherapy index regimens

Index HEC/MEC regimen (± LEC)	Emetogenicity	Number of recommended cycles[a]	Allowed gap (weeks)[b]	Regimen duration (weeks)
Breast cancer				
Cyclophosphamide (600 mg/m^2; with or without docetaxel)	If index dose >1,500 mg/m^2 then HEC[c]; if index dose ≤1,500 mg/m^2 then MEC[c]	4	3	12
Cyclophosphamide (600 mg/m^2)/doxorubicin (60 mg/m^2)	HEC[c]	4	3	12
Cyclophosphamide (600 mg/m^2)/doxorubicin (50 mg/m^2) + docetaxel	HEC[c]	6	3	18
Cyclophosphamide (600 mg/m^2)/doxorubicin (60 mg/m^2) + docetaxel	HEC[c]	4	3	12
Cyclophosphamide (600 mg/m^2)/doxorubicin (60 mg/m^2) + paclitaxel (R^1)	HEC[c]	4	2	8
Cyclophosphamide (600 mg/m^2)/doxorubicin (60 mg/m^2) + paclitaxel (R^2)	HEC[c]	4	3	12
Cyclophosphamide (500 mg/m^2)/doxorubicin (50 mg/m^2) + 5-fluorouracil	HEC[c]	6	3	18
Cyclophosphamide (100 mg/m^2)/epirubicin (830 mg/m^2)	HEC[c]	8	3	24
Cyclophosphamide (500 mg/m^2)/epirubicin (75 mg/m^2) + 5-fluorouracil	HEC[c]	4	3	12
Cyclophosphamide (500 mg/m^2)/epirubicin (100 mg/m^2) + docetaxel + 5-fluorouracil	HEC[c]	6	3	18
Cyclophosphamide (600 mg/m^2)/epirubicin (90 mg/m^2) + paclitaxel + 5-fluorouracil	HEC[c]	4	3	12
Carboplatin (500–900 mg/m^2; with docetaxel or trastuzumab or both)	MEC[c]	6	3	18
Carboplatin (150 mg) + paclitaxel	MEC[c]	3	1	3
Carboplatin (500 mg) + paclitaxel	MEC[c]	3	3	9
Carboplatin (150–900 mg/m^2) + gemcitabine	MEC[c]	6	3	18
Lung cancer				
Cisplatin (100 mg) + vinorelbine	If index dose ≥50 mg/m^2, then HEC[c]; if index dose <50 mg/m^2, then MEC[c]	4	4	16
Cisplatin (75–80 mg) + vinorelbine		4	3	12
Cisplatin (75 mg/m^2) + gemcitabine		4	3	12
Cisplatin (75 mg/m^2) + docetaxel		4	3	12
Cisplatin (75 mg/m^2) + etoposide		4	4	16
Cisplatin (75 mg/m^2) + pemetrexed		4	3	12
Carboplatin (150–900 mg/m^2) + etoposide	MEC[c]	6	4	24
Carboplatin (150–900 mg/m^2) + gemcitabine	MEC[c]	6	3	18
Carboplatin (500–900 mg/m^2) + docetaxel	MEC[c]	6	3	18
Carboplatin (500–900 mg) + paclitaxel	MEC[c]	3	3	9
Carboplatin (150–900 mg) + paclitaxel	MEC[c]	3	1	3
Colorectal cancer				
Oxaliplatin (85 mg/m^2) + 5-fluorouracil	MEC[c]	12	2	24
Oxaliplatin (85 mg/m^2) + 5-fluorouracil + leucovorin	MEC[c]	12	2	24
Oxaliplatin (130 mg/m^2) + capecitabine	MEC[c]	8	3	24

Notes: [a]As per NCCN guidelines at the time of the study[14–18] (the most recent NCCN guidelines indicate minor changes to the emetogenicity classification); [b]equal to the recommended cycle length as per NCCN guidelines[14–18]; [c]Hesketh rule in effect.[31] Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V2.2011, Colon Cancer V3.2011, Rectal Cancer V4.2011, Small Cell Lung Cancer V2.2012, Non-Small Cell Lung Cancer V3.2011. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. All accessed July 11, 2011. To view the most recent and complete version of the guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Abbreviations: HEC, highly emetogenic chemotherapy; MEC, moderately EC; LEC, lowly EC; EC, emetogenic chemotherapy; NCCN, National Comprehensive Cancer Network.

continuous data, and counts/relative frequencies were used for categorical data. Each baseline characteristic and study outcome was compared using unadjusted statistical tests between patients receiving palonosetron and those receiving all other 5-HT$_3$ RAs. Continuous variables were compared using Student's *t*-test or Wilcoxon rank-sum test, depending on the distributional characteristics. Categorical data were compared using χ^2 tests.

Logistic regression models were used to estimate associations between antiemetic treatment (palonosetron versus other 5-HT$_3$ RAs) and CINV (acute and/or delayed), delay of index chemotherapy regimen, and adherence to index chemotherapy regimen. Covariates in the multivariable regression analysis included age, sex, geographic region, health plan type, year of index date, cancer type, Deyo–Charlson Comorbidity Index (DCI) score,[32] individual comorbidities,

and baseline receipt of LEC, radiation, and antiemetics. All analyses were stratified by HEC and MEC regimens.

Results

Patient characteristics

We identified 1,832 HEC patients who received only palonosetron and no other 5-HT$_3$ RA and 2,387 HEC patients who received other 5-HT$_3$ RAs excluding palonosetron (Table 3). In the HEC group, the mean age was slightly higher among palonosetron users (52.0 versus 51.4 years for those receiving other 5-HT$_3$ RAs, P=0.0345), and breast cancer was the most common malignancy (97.3% palonosetron and 96.0% other 5-HT$_3$ RAs). The mean baseline DCI scores were 4.35 for patients receiving palonosetron and 4.56 for those receiving other 5-HT$_3$ RAs (P=0.0211). Similarly, we identified 1,350 palonosetron users and 1,379 other 5-HT$_3$ RA recipients who indexed on an MEC therapy. Within the MEC cohort, the mean age and DCI scores were slightly lower among palonosetron patients compared to those receiving other 5-HT$_3$ RAs (56.8 versus 59.2 years, P<0.0001; 4.29 versus 4.55, P=0.0229; respectively). Breast (48.6%) and colon (29.3%) cancers were the most prevalent malignancies among palonosetron recipients, whereas lung (35.2%) and colon (34.0%) cancers were more common among those receiving other 5-HT$_3$ RAs in the MEC group.

Incidence of CINV

Within the HEC cohort, fewer palonosetron patients experienced CINV compared with those who received other 5-HT$_3$ RAs (27.5% versus 32.2%, P=0.001; Table 4). Likewise, 19.1% and 14.8% of HEC patients receiving palonosetron experienced ≥1 acute and ≥1 delayed CINV event(s) respectively, compared to 20.5% and 20.2% of other 5-HT$_3$ RA HEC patients. Furthermore, patients in the other 5-HT$_3$ RA group experienced more CINV events per cycle than the palonosetron group (0.3 versus 0.2 events/cycle). In the MEC cohort, fewer palonosetron patients experienced CINV and CINV events per cycle compared with those who received other 5-HT$_3$ RAs (36.1% versus 41.7%, P=0.003; 0.3 versus 0.4 events/cycle). MEC patients in the palonosetron cohort were significantly less likely to experience delayed CINV versus patients in the other 5-HT$_3$ RA cohort (20.6% versus 29.5%, P<0.0001).

Chemotherapy treatment delay

Fewer chemotherapy treatment delays occurred among patients receiving palonosetron compared with other 5-HT$_3$ RAs in both the HEC (3.2% versus 6.0%, P<0.0001) and MEC (17.0% versus 26.8%, P<0.0001) cohorts (Table 4). The results for delayed therapy remained consistent when using the upper and lower limits as defined earlier (see Table 4). Mean time to delay was similar across the palonosetron and other 5-HT$_3$ RAs groups (approximately 76 days in the HEC cohort and 86 days in the MEC cohort).

Chemotherapy treatment adherence

In both the HEC and MEC cohorts, more patients receiving palonosetron were adherent to their chemotherapy regimen compared to those who received other 5-HT$_3$ RAs for three of the four different adherence measures. In the HEC cohort, slightly more of those who received palonosetron completed the recommended number of chemotherapy cycles versus those who received other 5-HT$_3$ RAs (87.7% versus 86.4%, respectively; P=0.2022). The difference was greater in the MEC cohort, with 65.6% of those receiving palonosetron and 59.8% of those receiving other 5-HT$_3$ RAs completing the recommended number of chemotherapy cycles (P=0.0017). Compared with those who received other 5-HT$_3$ RAs, significantly more patients receiving palonosetron completed the recommended number of chemotherapy cycles within the specified time frame (HEC, 74.7% versus 69.7%, respectively, P=0.0004; MEC, 43.1% versus 37.3%, respectively, P=0.0019) and at the expected doses (HEC, 27.3% versus 25.8%, respectively, P=0.0004; MEC, 15.0% versus 12.6%, respectively, P=0.0019) (Table 4). A similar proportion of patients in both the palonosetron and other 5-HT$_3$ RA cohorts received the recommended chemotherapy doses for HEC (33.6% palonosetron and 33.4% other 5-HT$_3$ RAs, P=0.8951) and MEC regimens (34.6% palonosetron and 37.1% other 5-HT$_3$ RAs, P=0.1673).

These findings were supported in a multivariable analysis (Figure 1). Treatment with palonosetron was associated with a reduced likelihood of CINV occurrence in the HEC (odds ratio [OR] 0.82, 95% CI 0.71–0.95) and MEC (OR 0.77, 95% CI 0.65–0.92) cohorts. Palonosetron treatment was also associated with fewer chemotherapy treatment delays in both cohorts (HEC, OR 0.63, 95% CI, 0.45–0.87; MEC, OR 0.74, 95% CI 0.60–0.91). Although palonosetron was associated with greater chemotherapy adherence in the HEC cohort (OR 1.25, 95% CI 1.07–1.45), no association was found in the MEC cohort (OR 1.1, 95% CI 0.92–1.32).

Discussion

In this retrospective, observational, nested case–control study, patients who received prophylactic or rescue palonosetron had significantly fewer CINV events, fewer chemotherapy

Table 3 Palonosetron versus other 5-HT_3 RAs among patients initiating an HEC/MEC regimen

Characteristics	HEC			MEC		
	Palonosetron group[a] n=1,832	Other 5-HT_3 RA group[b] n=2,387	*P*-value	Palonosetron group[a] n=1,350	Other 5-HT_3 RA group[b] n=1,379	*P*-value
Female, n (%)	1,805 (98.5)	2,333 (97.7)	0.0643	981 (72.7)	857 (62.2)	<0.0001
Age at index (years), mean ± SD	52.04 (±9.52)	51.41 (±9.6)	0.0345	56.82 (±10.9)	59.21 (±11.33)	<0.0001
18–44	394 (21.5)	571 (23.9)	0.1046	175 (13.0)	144 (10.4)	<0.0001
45–64	1,276 (69.7)	1,632 (68.4)		858 (63.6)	804 (58.3)	
≥65	162 (8.8)	184 (7.7)		317 (23.5)	431 (31.3)	
Geographic region, n (%)						
Northeast	288 (15.7)	278 (11.7)	<0.0001	185 (13.7)	173 (12.6)	<0.0001
South	585 (31.9)	736 (30.8)		445 (33.0)	480 (34.8)	
Midwest	651 (35.5)	488 (20.4)		485 (35.9)	406 (29.4)	
West	232 (12.7)	773 (32.4)		172 (12.7)	276 (20.0)	
Unknown	76 (4.2)	112 (4.7)		63 (4.7)	44 (3.2)	
Health plan type, n (%)						
HMO	314 (17.1)	487 (20.4)	0.0047	238 (17.6)	278 (20.2)	0.0115
POS	99 (5.4)	85 (3.6)		49 (3.6)	34 (2.5)	
PPO	1,286 (70.2)	1,661 (69.6)		898 (66.5)	879 (63.7)	
FFS	12 (0.7)	15 (0.6)		7 (0.5)	21 (1.5)	
Other/unknown	121 (6.6)	139 (5.8)		158 (11.7)	167 (12.1)	
Medicare plan[c]	134 (7.3)	190 (8.0)	0.4352	233 (17.3)	353 (25.6)	<0.0001
Index year, n (%)						
2002–2004	16 (0.9)	736 (30.8)	<0.0001	8 (0.6)	105 (7.6)	<0.0001
2005–2006	936 (51.1)	924 (38.7)		343 (25.4)	515 (37.4)	
2007–2008	854 (46.6)	670 (28.1)		963 (71.3)	685 (49.7)	
2009–2011	26 (1.4)	57 (2.4)		36 (2.7)	74 (5.4)	
Baseline medical conditions, n (%)						
Breast cancer	1,782 (97.3)	2,291 (96.0)	0.0228	656 (48.6)	425 (30.8)	<0.0001
Lung cancer	50 (2.7)	96 (4.0)	0.0228	299 (22.2)	485 (35.2)	<0.0001
Colorectal cancer	0	0	NA	395 (29.26)	469 (34.0)	0.0076
Hypertension	679 (37.1)	871 (36.5)	0.7015	700 (51.9)	751 (54.5)	0.1722
Cerebrovascular disease	33 (1.8)	47 (2.0)	0.6922	80 (5.9)	101 (7.3)	0.1422
Heart failure	26 (1.4)	39 (1.6)	0.5748	49 (3.6)	76 (5.5)	0.0187
Renal disease[d]	35 (1.9)	46 (1.9)	0.9689	60 (4.4)	63 (4.6)	0.8759
Liver disease	28 (1.5)	34 (1.4)	0.7808	40 (3.0)	36 (2.6)	0.5759
Diabetes mellitus	174 (9.5)	194 (8.1)	0.1179	216 (16)	226 (16.4)	0.7829
Ischemic heart disease	84 (4.6)	107 (4.5)	0.8738	165 (12.2)	238 (17.3)	0.0002
Pulmonary disease[e]	211 (11.5)	297 (12.4)	0.3602	315 (23.3)	460 (33.4)	<0.0001
Osteoporosis	197 (10.8)	244 (10.2)	0.5761	149 (11.0)	149 (10.8)	0.8459
Mental health disorder	441 (24.1)	543 (22.8)	0.3135	352 (26.1)	375 (27.2)	0.5083
DCI score						
Mean ± SD	4.35 (±2.92)	4.56 (±2.98)	0.0211	4.29 (±2.88)	4.55 (±2.95)	0.0229
Median (Q1–Q3)	2 (2–8)	3 (2–8)	0.0264	3 (2–8)	3 (2–8)	0.0002
Baseline therapies, n (%)						
LEC	93 (5.1)	108 (4.5)	0.4042	193 (14.3)	205 (14.9)	0.6734
Radiation	60 (3.3)	113 (4.7)	0.0179	237 (17.6)	290 (21.0)	0.0215
5-HT_3 antiemetics	675 (36.8)	895 (37.5)	0.6652	450 (33.3)	374 (27.1)	0.0004
Non-5-HT_3 antiemetics	1,166 (63.7)	1,359 (56.9)	<0.0001	828 (61.3)	728 (52.8)	<0.0001
Chemotherapeutic regimens, n (%)						
Cyclophosphamide	6 (0.3)	7 (0.3)		499 (37.0)	287 (20.8)	
Cyclophosphamide/doxorubicin	1,656 (90.4)	2,133 (89.4)				
Cyclophosphamide/epirubicin	120 (6.6)	151 (6.3)				
Cisplatin	50 (2.7)	96 (4.0)		21 (1.6)	13 (0.9)	
Carboplatin				435 (32.2)	610 (44.2)	
Oxaliplatin				395 (29.3)	469 (34.0)	

(*Continued*)

Table 3 (*Continued*)

Characteristics	HEC			MEC		
	Palonosetron group[a] n=1,832	Other 5-HT$_3$ RA group[b] n=2,387	*P*-value	Palonosetron group[a] n=1,350	Other 5-HT$_3$ RA group[b] n=1,379	*P*-value
Duration of study follow-up, days						
Mean ± SD	1,239.79 (±521.83)	1,398.59 (±722.88)	<0.0001	1,036.1 (±414.11)	1,089.16 (±517.92)	0.0031
Median (Q1–Q3)	1,200 (835.5–1,648.5)	1,295 (807–1,885)	<0.0001	994.5 (716–1,270)	1,013 (648–1,407)	0.1939

Notes: [a]Receipt of palonosetron and no other 5-HT$_3$ RA during any cycle, measured from (HEC cycle-start date −1 day) until (HEC cycle-start date +5 days); [b]receipt of any 5-HT$_3$ RA except palonosetron during any cycle, measured from (chemotherapy cycle-start date −1 day) until (chemotherapy cycle start date +5 days); [c]consisting of Medicare Advantage, supplemental, and Part D plans; [d]renal disease included kidney disease, nephrosis, nephritis, and renal function impairment, including dialysis; [e]pulmonary disease included asthma, bronchitis, pneumonia, emphysema, and COPD.

Abbreviations: HT, hydroxytryptamine; RAs, receptor antagonists; HEC, highly EC; MEC, moderately EC; LEC, lowly EC; NEC, non-EC; EC, emetogenic chemotherapy; SD, standard deviation; HMO, health maintenance organization; POS, point of service; PPO, preferred provider organization; FFS, fee for service; NA, not applicable; Q, quartile; COPD, chronic obstructive pulmonary disease; DCI, Deyo–Charlson Comorbidity Index.

treatment delays, and higher adherence to their chemotherapy regimen compared with patients who received any other IV 5-HT$_3$ RA medication. These findings were seen both among patients who were undergoing HEC treatment and those undergoing MEC treatment.

Results from clinical trials have demonstrated the overall efficacy of palonosetron in preventing acute CINV in patients receiving HEC and in preventing acute or delayed CINV in patients receiving MEC.[20,24–26] However, limited evidence is available regarding the effect of palonosetron on chemotherapy adherence and treatment delay in a real-world setting. To our knowledge, no previous study has evaluated this association. A previous administrative claims analysis evaluated the risk of serious CINV events associated with

Table 4 Outcomes among palonosetron versus other 5-HT$_3$ RAs in patients initiating an HEC/MEC regimen

Outcomes of interest	HEC			MEC		
	Palonosetron group n=1,832	Other 5-HT$_3$ RA group n=2,387	*P*-value	Palonosetron group n=1,350	Other 5-HT$_3$ RA group n=1,379	*P*-value
CINV						
Patients experiencing ≥1 CINV event, n (%)	504 (27.5)	768 (32.2)	0.0011	487 (36.1)	575 (41.7)	0.0026
Patients experiencing ≥1 acute CINV event	350 (19.1)	490 (20.53)	0.2513	361 (26.74)	334 (24.22)	0.1308
Patients experiencing ≥1 delayed CINV event	271 (14.79)	482 (20.19)	<0.0001	278 (20.59)	407 (29.51)	<0.0001
Total number of cycles	7,616	9,878		7,952	8,749	
Total number of events	1,552	2,685		2,070	3,686	
Acute	769	1,212		1,193	1,196	
Delayed	783	1,473		877	2,490	
Events/cycle	0.2038	0.2718		0.2603	0.4213	
Treatment delay						
Treatment delay, n (%)	59 (3.2)	144 (6.0)	<0.0001	230 (17.0)	369 (26.8)	<0.0001
Treatment delay, lower limit, n (%)	102 (5.6)	199 (8.3)	0.0005	363 (26.9)	536 (38.9)	<0.0001
Treatment delay, upper limit, n (%)	19 (1.0)	40 (1.7)	0.08	101 (7.5)	163 (11.8)	0.0001
Therapy length until delay (days)						
Mean (± SD)	76.28 (±22.65)	76.32 (±22.62)	0.9577	87.38 (±42.45)	85.45 (±48.18)	0.2659
Median (Q1–Q3)	67 (64–85)	76 (64–85)	0.0147	85 (62–111)	85 (48–126)	0.0147
Treatment adherence, n(%)						
Receipt of						
1. Recommended number of cycles	1,607 (87.7)	2,062 (86.4)	0.2022	885 (65.6)	824 (59.8)	0.0017
2. Recommended number of cycles within the specified time frame	1,368 (74.7)	1,664 (69.7)	0.0004	582 (43.1)	514 (37.3)	0.0019
3. Recommended number of cycles within the specified time frame at the expected dose	500 (27.3)	616 (25.8)	0.0004	202 (15.0)	173 (12.6)	0.0019
4. Recommended dose	616 (33.6)	798 (33.4)	0.8951	467 (34.6)	512 (37.1)	0.1673

Abbreviations: HT, hydroxytryptamine; RAs, receptor antagonists; HEC, highly EC; MEC, moderately EC; EC, emetogenic chemotherapy; CINV, chemotherapy-induced nausea/vomiting; SD, standard deviation; Q, quartile.

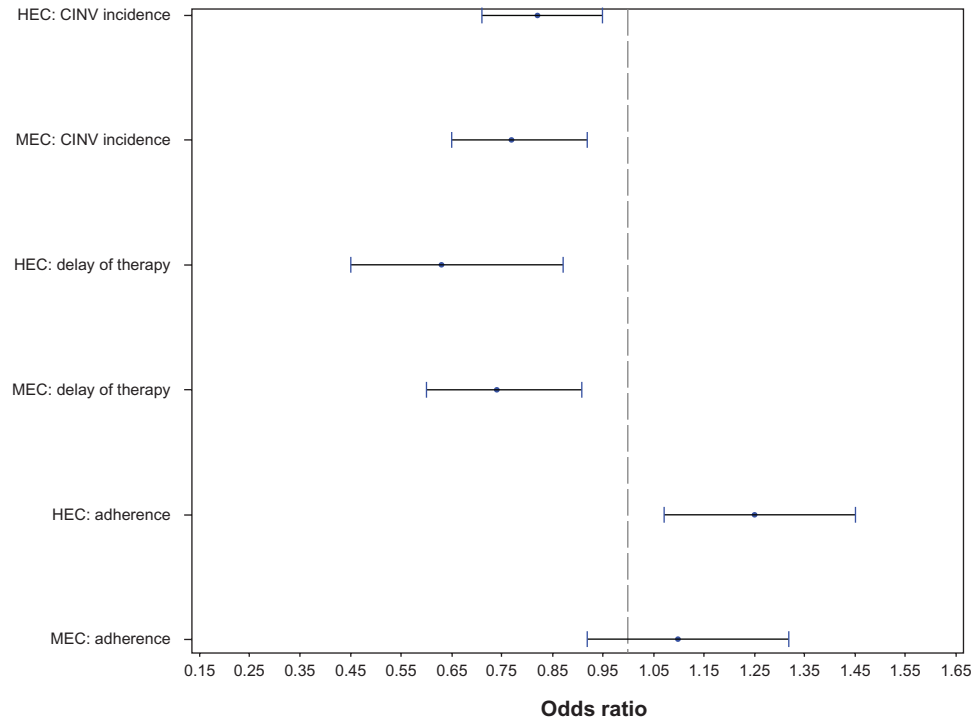

Figure 1 Odds ratios and 95% confidence intervals for palonosetron versus other 5-HT^3-RAs.
Notes: For CINV and delayed therapy, an odds ratio <1 is associated with improved outcomes; for adherence, an odds ratio >1 is associated with improved outcomes.
Abbreviations: HT, hydroxytryptamine; CINV, chemotherapy-induced nausea/vomiting; HEC, highly EC; MEC, moderately EC; EC, emetogenic chemotherapy.

hospital or emergency department admissions among patients with breast or lung cancer undergoing MEC or HEC who received palonosetron compared with those who received any other 5-HT$_3$ RA.[19] Patients receiving palonosetron experienced a significantly reduced risk of serious CINV compared to those who received other 5-HT$_3$ RAs, ranging from 31% to 45% among lung and breast cancer patients, respectively. Another recent study by Craver et al evaluated the risk of CINV among recipients of palonosetron versus other 5-HT$_3$ RAs initiating HEC/MEC therapy in all medical settings,[28] using a broader definition of CINV encompassing events occurring any time within 7 days of the chemotherapy cycle-start date. While both studies showed a reduction in CINV with palonosetron use as expected, an exploration of the effect of CINV risk reduction on chemotherapy adherence or delay was not conducted.

The real-world analysis in the current study demonstrated improved adherence to chemotherapy regimens among patients who received palonosetron compared with other 5-HT$_3$ RA agents. The association between the use of antiemetics and adherence may have been underestimated: patients undergoing chemotherapy, particularly HEC, are more likely to have been prepared by their health care providers to expect nausea and vomiting; such preparedness has been shown to alleviate the reported incidence of nausea and vomiting in patients receiving chemotherapy.[31] Additionally, some patients undergoing IV chemotherapy regimens will have advanced disease, and may therefore not have the option of delaying or discontinuing treatment because of nausea and vomiting.[33]

Future research exploring the association between reduced CINV and chemotherapy adherence would benefit from a cost analysis, which was not included in the current study. A therapy that improves chemotherapy adherence by reducing CINV events could potentially reduce costs, both direct (costs of antiemetic medications, physician visits, and hospitalizations) and indirect (lost workdays and intangibles, including lower quality of life and potential consequences of delayed or reduced chemotherapy treatment). Other chemotherapy-associated side effects, such as fatigue, insomnia, or dermatologic conditions, which cannot be easily identified through claims, may also affect treatment adherence.

The nature of the administrative claims database and the lack of granularity precluded us from identifying more than one CINV event per day or the severity of the CINV experienced. While our approach to identify CINV events from claims matches that used in clinical trials of antiemetics,[19,28] others have used criteria that were either more strict (eg, nausea, vomiting, and dehydration associated with hospital admissions[27]) or that relied on patient diaries rather than

diagnosis codes.[24,25] The strategy used in the current study to define CINV did not capture patients using oral antiemetics or over-the-counter remedies, and the IV antiemetics may have been prescribed for reasons other than CINV (eg, for nausea and vomiting associated with migraine,[34] surgery,[35] or gastroparesis[36]). Nausea and vomiting occurring after day 5 of the chemotherapy cycle and before the subsequent cycle were not attributed to chemotherapy, and may have resulted in an underestimation of CINV events. Despite these limitations, the narrow time frame and broader medical setting used for identifying CINV in the current study design resulted in a conservative estimate of the impact of palonosetron and other 5-HT$_3$ RAs on CINV in a real-world setting.

Administrative claims are designed for reimbursement rather than research, and may contain coding errors or omissions. Therefore, the claim-based algorithm developed to identify patients with early stage cancers may be susceptible to potential misidentification. Furthermore, standard definitions of adherence with IV chemotherapy regimens within an administrative claim database are lacking in the published literature. All patients were members of large commercial health plans in the US; the results may not be generalizable to patients outside the US or with other types of health insurance. While enrollment was limited to patients with single-day chemotherapy regimens, further research in patients receiving multiday regimens would be desirable. Because of concerns regarding patient selection and cohort size, the comparative analysis was limited to IV chemotherapy in general and IV 5-HT$_3$ RAs as a class. Consistent with NCCN guideline recommendations, the analysis assumed that the non-5-HT$_3$ RA components of the observed antiemetic regimens were similar across the palonosetron and other cohorts. NCCN guidelines were used to define chemotherapy regimens for this analysis, and did not allow for individualized treatment plans. BSA was needed to calculate the index dosage of cyclophosphamide and cisplatin; however, this information is unavailable in administrative claims. In the absence of US-based data, BSA estimates developed in a prior UK study[30] were used to calculate index doses.

Conclusion

In this real-world retrospective analysis, patients receiving palonosetron were more adherent to their HEC/MEC regimens and experienced fewer treatment delays compared to patients receiving other 5-HT$_3$ RAs. Palonosetron was also associated with a decrease in the occurrence of CINV events. These results highlight the importance of symptom control in the context of adherence to prescribed chemotherapy, which may ultimately influence treatment and disease outcomes, including costs. This study also presents an innovative approach to estimate adherence to IV chemotherapy using administrative claims data.

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Disclosure

SRP was an employee of HealthCore at the time of the study, and MG and RAQ are current employees of HealthCore, an independent research organization that received funding from Eisai Pharmaceuticals for the conduct of this study. HSR is a consultant to Eisai Pharmaceuticals. SRP is now an employee of CTI Clinical Trial and Consulting Services, Cincinnati, OH, USA.

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Supplementary materials

Assignment of index chemotherapy regimens

Identification of chemotherapeutic regimens involves a two-step process. Step one involves the identification of the highly emetogenic chemotherapy (HEC)/moderately EC (MEC) agents making up the regimen, which are identified within 6 days of the index date. For instance, for a breast cancer patient with a claim for cyclophosphamide on the index date (ie, the start date of the first chemotherapy cycle), medical and pharmacy claims are evaluated to determine the presence of another HEC/MEC drug (eg, doxorubicin, epirubicin, etc). If no other HEC/MEC drug is found, then the index dose is calculated by using the strength (as determined from the index medical or pharmacy claim) and the body surface-area estimate. A dose of $>$1,500 mg/m^2 indicates receipt of HEC, while an index dose $\leq$1,500 mg/m^2 indicates MEC. However, if doxorubicin is present, then the patient is classified as HEC as per the Hesketh algorithm.[31] Step two of the chemotherapy-regimen identification involves claims for non-HEC/MEC chemotherapy agents also observed within 6 days of the index date (Table S3). In the aforementioned example, for a patient indexing on cyclophosphamide and doxorubicin, if a claim for another lowly EC or non-EC drug (eg, docetaxel, paclitaxel, etc) is found within ±6 days of the index date, then the patient's adherence will be evaluated as per the NCCN Guidelines® recommendations for the appropriate cyclophosphamide/doxorubicin/docetaxel combination regimen. Where multiple regimen options were available for the drugs involved, additional analysis was performed to determine the specific regimen. This included determining the doses of the HEC/MEC components in order to pinpoint the specific regimen. For example, a doxorubicin dose of 50 and 60 mg/m^2 would indicate a regimen involving six and four cycles, respectively (Table 2). Duration between the claims for the index HEC/MEC drugs was also used if the doses were insufficient in differentiating among the various regimen options. A combination involving cyclophosphamide/doxorubicin/paclitaxel could be assigned a regimen either 8 weeks or 12 weeks long if the gap between the first and second claim for cyclophosphamide/doxorubicin was found to be 14 or 21 days, respectively.

Table S1 CINV codes and antiemetic therapies

Generic name	GPI	HCPCS	ICD-9-CM diagnosis
5-HT$_3$ RAs			
Dolasetron mesylate	50250025x	J1260, Q0180	
Granisetron	50250035x	J1626, Q0166	
Ondansetron	50250065x	J2405, Q0179	
Palonosetron	50250070x	J2469	
Other antiemetics			
Dexamethasone	22100020x	J1094, J1100, J7637, J7638, J7312, J8540	
Fosaprepitant	502800351021x	J1453	
Promethazine	41400020101210, 414000201020x, 414000201003x, 41400020101215, 414000201029x, 414000201052x	J2550, J2180, Q0169, Q0170	
Prochlorperazine	59200055x	J0780, Q0164, Q165, S0183	
Metoclopramide	523000201020x, 523000201003x, 523000201012x, 523000201013x, 523000201029x, 523000201072x, 523000201 1x	J2765	
Lorazepam	571000600020x, 571000600003x, 571000600013x	J2060	
Haloperidol	5910001030x, 591000102020x, 5910001010x, 591000102013x	J1630, J1631	
Diphenhydramine	4120003010x, 412000303x, 60300020x, 6030990x	J1200, Q0163	
Nausea			
Nausea and vomiting	22100020x	J1094, J1100, J7637, J7638, J7312, J8540	787.0x
Persistent vomiting	5028002000x	J8501	536.2x
Volume depletion	502800351021x	J1453	276.5x
Hydration (nontherapeutic administration)		96360, 96361, 90760, 90761, 2018F, G0345	

Abbreviations: CINV, chemotherapy-induced nausea/vomiting; HT, hydroxytryptamine; RAs, receptor antagonists; GPI, generic product identifier; HCPCS, Healthcare Common Procedure Coding System; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.

Table S2 Chemotherapy codes and emetogenic potential

Description	GPI code	HCPCS code	Emetogenicity	Formulation
Carmustine	21102010x	J9050, C9437	Other	IV
Cisplatin	211000200020x	J9060, J9062, C9418	Other	IV
Dacarbazine	2170002000x	J9130, J9140, C9423	HEC	IV
Mechlorethamine	211010301021x	J9230	HEC	IV
Streptozotocin	21102030002105	J9320	HEC	IV
Alemtuzumab	21353010x	J9010	Minimal	IV
Arsenic trioxide	21700008x	J9017	MEC	IV
Azacitidine	21300003x	J9025	MEC	IV
Bendamustine	21100009x	J9033	MEC	IV
Carboplatin	21100015x	J9045	MEC	IV
Clofarabine	21300008x	J9027, C9129	MEC	IV
Dactinomycin	212000200021x	J9120	MEC	IV
Daunorubicin	21200030x	J9150–J9151, C9424	MEC	IV
Doxorubicin	21200040x	J9000–J9001, C9415	Other	IV
Epirubicin	21200042x	J9178, J9180	Other	IV
Idarubicin	21200045x	J9211, C9429	MEC	IV
Ifosfamide	2110102500x, 219900024064x	J9208, C9427	Other	IV
Irinotecan	21550040x	J9206	MEC	IV
Melphalan	211010400021x, 211010401021x	J9245	MEC	IV
Oxaliplatin	21100028x	J9263, C9205	MEC	IV
Temozolomide	211040700021x	J9328, C9253	MEC	IV
Aldesleukin	21703020x	J9015	Other	IV
Amifostine crystalline	21758010x	J0207	Other	IV
Cyclophosphamide	21101020002x	J9070–J9097, C9420, C9421	Other	IV
Cytarabine	21300010x	J9098–J9110, C9422	Other	IV
Interferon-α	217000601x, 217000602x, 217000603x	J9212–J9215	Other	IV
Altretamine	21100005x		MEC/HEC	Oral
Procarbazine	21700050x	S0182	MEC/HEC	Oral
Cyclophosphamide	211010200003x	J8530	Other	Oral
Imatinib	21534035x	S0088	Minimal/Low	Oral
Temozolomide	211040700001x	J8700	Other	Oral
Busulfan	211000100003x	J0594, J8510	Other	Oral
Estramustine phosphate sodium	2140302010x		MEC/HEC	Oral
Etoposide	21500010x	J8560	MEC/HEC	Oral
Lomustine	211020200001x	S0178	MEC/HEC	Oral

Notes: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Antiemesis, Version 1.2012. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. Accessed August 11, 2011. To view the most recent and complete version of the guideline, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. Other = NCCN emetogenicity rating depends on dosage.

Abbreviations: GPI, generic product identifier; HCPCS, Healthcare Common Procedure Coding System; HEC, highly EC; MEC, moderately EC; EC, emetogenic chemotherapy; IV, intravenous.

Table S3 HEC/MEC regimens

Agent	Regimen	Schedule	Regimen type	MEC/HEC
Cyclophosphamide	TC	• Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 3 weeks for four cycles	Single day	Depends on dosage
Cyclophosphamide/ doxorubicin	TAC (with docetaxel)	• Doxorubicin 50 mg/m^2 IV day 1 • Cyclophosphamide 500 mg/m^2 IV day 1 Cycled every 3 weeks for six cycles	Single day	HEC
	TAC (with docetaxel)	• Doxorubicin 60 mg/m^2 on day 1 • Cyclophosphamide 500 mg/m^2 IV day 1 Cycled every 3 weeks for four cycles	Single day	HEC
	AC	• Doxorubicin 60 mg/m^2 IV day 1 • Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 2 weeks for four cycles	Single day	HEC
		• Doxorubicin 60 mg/m^2 IV day 1 • Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 3 weeks for four cycles	Single day	HEC
		• Doxorubicin 60 mg/m^2 IV day 1 • Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 3 weeks for four cycles	Single day	HEC
		• Doxorubicin 60 mg/m^2 IV day 1 • Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 3 weeks for four cycles	Single day	HEC
	FAC/CAF (with 5-FU)	• Doxorubicin 50 mg/m^2 IV day 1 • Cyclophosphamide 500 mg/m^2 IV day 1 Cycled every 3 weeks for six cycles	Single day	HEC
Cyclophosphamide/ epirubicin	FEC/CEF (with 5-FU)	• Epirubicin 75 mg/m^2 IV day 1 • Cyclophosphamide 500 mg/m^2 day 1 Cycled every 3 weeks for four cycles	Single day	HEC
	EC	• Epirubicin 100 mg/m^2 IV day 1 • Cyclophosphamide 830 mg/m^2 IV day 1 Cycled every 3 weeks for eight cycles	Single day	HEC
	FEC	• Epirubicin 100 mg/m^2 IV day 1 • Cyclophosphamide 500 mg/m^2 day 1 Cycled every 3 weeks for three cycles	Single day	HEC
	FEC	• Epirubicin 90 mg/m^2 IV day 1 • Cyclophosphamide 600 mg/m^2 IV day 1 Cycled every 3 weeks for four cycles	Single day	HEC
Carboplatin	TCH	• Carboplatin AUC 6 IV day 1 Cycled every 3 weeks for six cycles	Single day	MEC
	CH (with trastuzumab)	• Carboplatin AUC 6 IV day 1 Cycled every 3 weeks for six cycles	Single day	MEC
	CT (with docetaxel)	• Carboplatin AUC 6 IV day 1 Cycled every 3 weeks for six cycles	Single day	MEC
Cisplatin	CV (with vinorelbine)	• Cisplatin 100 mg/m^2 day 1 Cycled every 4 weeks for four cycles	Single day	HEC/depends on dosage
	CV (with vinorelbine)	• Cisplatin 75–80 mg/m^2 day 1 Cycled every 3 weeks for four cycles	Single day	HEC/depends on dosage
	CG (with gemcitabine)	• Cisplatin 75 mg/m^2 day 1 Cycled every 3 weeks for four to six cycles	Single day	HEC/depends on dosage
	CD (with docetaxel)	• Cisplatin 75 mg/m^2 day 1 Cycled every 3 weeks for four to six cycles	Single day	HEC/depends on dosage
	CP (with pemetrexed)	• Cisplatin 75 mg/m^2 day 1 Cycled every 3 weeks for four cycles	Single day	HEC/depends on dosage
Carboplatin	PC (with paclitaxel)	• Carboplatin AUC 6 day 1 Cycled every 3 weeks for four to six cycles	Single day	MEC
	PC (with paclitaxel)	• Carboplatin AUC 2 (initial) and 6 (last 2) weekly Total of three cycles	Single day	MEC

(*Continued*)

Table S3 (*Continued*)

Agent	Regimen	Schedule	Regimen type	MEC/HEC
	PG (with gemcitabine)	• Carboplatin AUC 2 day 1 Cycled every 3 weeks for six cycles	Single day	MEC
	PE (with etoposide)	• Carboplatin AUC 2 day 1 Cycled every 4 weeks for six cycles	Single day	MEC
Oxaliplatin	FOLFOX	• Oxaliplatin 85 mg/m^2 day 1 Cycled every 2 weeks for 6 months	Single day	MEC
	FOLFOX (modified)	• Oxaliplatin 85 mg/m^2 day 1 Cycled every 2 weeks for 6 months	Single day	MEC
	XELOX	• Oxaliplatin 130 mg/m^2 day 1 Cycled every 3 weeks for eight cycles	Single day	MEC

Note: Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V2.2011, Colon Cancer V3.2011, Rectal Cancer V4.2011, Small Cell Lung Cancer V2.2012, Non-Small Cell Lung Cancer V3.2011 [All accessed July 11, 2011], Antiemesis V1.2012 [Accessed August 11, 2011]. © National Comprehensive Cancer Network, Inc 2015. All rights reserved. To view the most recent and complete version of the guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.

Abbreviations: MEC, moderately emetogenic chemotherapy; HEC, highly EC; TC, taxotere/cyclophosphamide; IV, intravenous; TAC, Docetaxel/doxorubicin/cyclophosphomide; AC, Doxorubicin/cyclophosphomide; FAC/CAF, Flurouracil/doxorubicin/cyclophosphomide; 5-FU, 5-fluorouracil; FEC/CEF, Cyclophosphomide/Epirubicin/ Flurouracil; TCH, Docetaxel/carboplatin/trastuzumab; CH, Docetaxel/carboplatin/trastuzumab; CT, Carboplatin/trastuzumab; CV, Cisplatin/vinorelbine; CG, Cisplatin/gemicitabine; CD, Cisplatin/docetaxel; CP, Cisplatin/pemetrexed; PC, Paclitaxel/Carboplatin; PG, Paclitaxel/Carboplatin/gemicitabine; PE, Paclitaxel/Carboplatin/etoposide; FOLFOX, Folinic acid/Fluorouracil/Oxaliplatin; XELOX, Capecitabine/Oxaliplatin.