Original Article

Efficacy of the combination neurokinin-1 receptor antagonist, palonosetron, and dexamethasone compared to others for the prophylaxis of chemotherapy-induced nausea and vomiting: a systematic review and meta-analysis of randomized controlled trials

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Background: Chemotherapy-induced nausea and vomiting (CINV), a common side effect of chemotherapy, can substantially impair a patient's quality of life, interfere with a patient's compliance with anticancer therapy, and result in the manifestation of adverse events such as electrolyte imbalance, dehydration and malnutrition. The most recent guidelines published by the Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) recommend the combination of dexamethasone (DEX), a 5-hydroxytrypatmine-3 receptor antagonist (5-HT3RA), preferably palonosetron (PALO), and a neurokinin-1 receptor antagonist (NK1RA) for prophylactic treatment of CINV in patients receiving highly emetogenic chemotherapy (HEC). The aim of this review was to examine the efficacy of triple agent, as reported in randomized controlled trials (RCTs), compared to any other prophylactic treatments.

Methods: A literature search was conducted in Ovid MEDLINE(R), Embase Classic & Embase, and the Cochrane Central Register of Controlled Trials. The primary endpoint was the proportion of patients achieving complete response (CR) in the acute, delayed and overall phase. Secondary endpoints included the percentage of patients who achieved complete control (CC), no nausea and no vomiting in the acute, delayed and overall phases.

Results: A total of 17 RCTs were included in this review, of which 3,146 patients were randomized to receive NK1RA, PALO and DEX, and 2,987 patients to receive other antiemetic treatments. The combination was not superior to other treatments in five endpoints—CC and CR in the acute phase, nausea and emesis control in the delayed phase, and nausea in the overall phase—but was superior in the other 11 endpoints. When looking only at HEC and moderately emetogenic chemotherapy (MEC) studies, the combination was only superior to others in three endpoints (delayed and overall CC, and overall emesis control) in HEC setting, which is less than the nine identified endpoints (delayed and overall CR, delayed and overall CC, acute and overall nausea control, and acute, delayed and overall phases for emesis control) in the MEC setting.

Conclusions: The combination of NK1RA, PALO and DEX is superior in the majority of assessed endpoints of this meta-analysis. Further studies should investigate the efficacy and safety of the triple regimen compared to regimens lacking NK1RA, to add to the discussions about whether future CINV prophylaxis guidelines should include NK1RA as a first-line treatment in the MEC setting.

Keywords: Chemotherapy-induced nausea and vomiting (CINV); efficacy; safety; palonosetron (PALO); neurokinin-1 (NK1); dexamethasone (DEX); anti-emetic

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Introduction

Chemotherapy-induced nausea and vomiting (CINV), a common side effect of systemic anticancer therapy, can substantially impair a patient's quality of life, interfere with a patient's compliance with anticancer therapy, and result in complications such as electrolyte imbalance, dehydration and malnutrition (1-7). Investigating the safety and efficacy of antiemetics is hence crucial to ameliorating outcomes of cancer patients (8).

Two principal neurotransmitters that are involved in the pathogenesis of CINV are serotonin [5-hydroxytrypatmine 3 (5-HT_3)] and substance P (9). Serotonin from enterochromaffin cells in the small intestines can bind to 5-HT_3 receptors on vagal afferents and induce CINV (10). Substance P found in vagal afferent neurons can initiate signals to the vomiting centre in the lateral reticular formation of the medulla through bindind to neurokinin-1 (NK_1) receptors and induce vomiting (11,12). In an effort to reduce the occurrence of CINV, 5-HT_3-serotonin antagonists (5-HT_3RA) and neurokinin-1 receptor antagonists (NK_1RA) have been developed.

Randomized controlled trials (RCTs) have studied several 5-HT_3RAs with respect to efficacy (10,13-15); a systematic review and meta-analysis by Popovic et al suggested that palonosetron (PALO) is superior in terms of efficacy and safety when compared to other 5-HT_3RAs (16). The combination of multiple antiemetic medications targeting different molecular pathways associated with CINV, in addition to PALO, has become the standard of care of prophylactic treatment.

The guidelines published by the Multinational Association of Supportive Care in Cancer (MASCC) and European Society of Medical Oncology (ESMO) (17), National Comprehensive Cancer Network (NCCN) (18) and American Society of Clinical Oncology (ASCO) (19) recommend the combination of dexamethasone (DEX), and a 5-HT_3RA, for prophylaxis of CINV in patients receiving moderately emetogenic chemotherapy (MEC). For those patients undergoing highly emetogenic chemotherapy (HEC) treatment, the addition of a NK_1RA to the regimen of DEX and 5-HT_3RA has been recommended for prophylaxis of CINV by MASCC/ESMO; ASCO and NCCN recommends a quadruple-regimen consisting of olanzapine (OLAN), NK_1RA, DEX and a 5-HT_3RA.

Previous RCTs and a meta-analysis have studied whether a triple regimen (NK_1RA, PALO and DEX) is superior in terms of efficacy, compared to the two-medication regimen (PALO and DEX) (8,20). The meta-analysis suggested that the triple regimen is statistically superior to DEX and PALO in 11 of 12 CINV endpoints (8). The review consisted of four studies; several new RCTs have been published since the previous meta-analysis. Additionally, it only compared triple-regimen with double-regimen antiemetic treatments, which limited the statistical power of the review. The purpose of this review was to examine the efficacy of NK_1RA, PALO and DEX as reported in RCTs compared to any other prophylactic CINV treatments.

Methods

Search strategy

A literature search was conducted in Ovid MEDLINE(R) (1946 to June Week 4 2017), Embase Classic & Embase (1947 to 2017 Week 27), and the Cochrane Central Register of Controlled Trials (May 2017). MeSH terms, Emtree terms and free text keywords such as "neoplasms" "chemotherapy" "nausea" "vomiting" "palonosetron" and "neurokinin 1 receptor antagonist" were used to prompt relevant literature; the search was also limited to English language clinical trials (*Table S1*). Reference lists of included RCTs and past meta-analyses were also searched. Titles and abstracts were screened to identify studies relevant for full-text review, and full-text review identified studies eligible for this review based on a pre-specified inclusion criterion.

Selection criteria

Titles and proceeding were selected for inclusion if they

suggested that the study: (I) was a randomized trial; (II) had one intervention arm consisting of at least NK_1RA, PALO and DEX for the prophylaxis of CINV; (III) relevant study data was extractable.

Studies were included if at least one endpoint [complete response (CR), complete control (CC), no nausea, no vomiting] in the acute, delayed or overall phases was available. The definition of the endpoints for this review are: (I) CR—no emesis and no use of rescue antiemetics; (II) CC—no emesis, no rescue medication and no more than mild nausea; (III) no nausea—no episodes of nausea; (IV) no vomiting—no episodes of vomiting; (V) acute phase—0 to 24 hours after chemotherapy; (VI) delayed phase—24 to 120 hours after chemotherapy; (VII) overall phase—0 to 120 hours after chemotherapy.

Studies were excluded if they were duplicates of articles found in each database, non-original research reports or small trials (<five patients).

Data extraction and endpoints

The primary endpoint was the proportion of patients achieving CR in the acute, delayed and overall phase. Secondary endpoints included the proportion of patients who achieved CC, no nausea and no vomiting in the acute, delayed and overall phases. Studies must have explicitly reported distinct acute, delayed or overall endpoints. Efficacy data from studies with more than two arms were pooled to compare the combination of NK_1RA, PALO and DEX to the numerous other interventions. Endpoints from different cycles were not pooled together. The sample size of each intervention arm was calculated from the randomization ratio when the sample size of the arms was not explicitly reported.

Statistical analyses

Statistical analyses were performed using Review Manager (RevMan 5.3) by Cochrane IMS. The Mantel-Haenszel method was applied and a random-effects analysis model was used to calculate odds ratio (OR), absolute risk differences (RD) and accompanying 95% confidence intervals (CI). RDs were compared to the 2016 MASCC/ESMO antiemetic guidelines, which noted "*as a general rule, the panel considered changes of 10% or greater to be sufficient to warrant the changing of a recommendation*" (17).

Trials were stratified based on the authors' report of chemotherapy emetogenicity – trials comprised of only HEC patients and only MEC patients. Subgroup analyses were conducted within these subgroups to study the efficacy of NK_1RA, PALO and DEX; each subgroup had accompanying OR, RD and 95% CI.

Results

The literature search identified 359 records, and an additional 26 records were identified from the reference lists of included RCTs and previous meta-analyses. After 147 duplicates were removed, a total of 238 title and abstracts were screened for eligibility. Ultimately, 17 RCTs were included in this review (20-36), of which 3,597 patients were randomized to receive NK_1RA, PALO and DEX, and 3,438 patients to receive other antiemetic treatments (*Figure S1*).

Of the 17 included studies, 12 investigated antiemetic efficacy in patients receiving HEC, while five only studied MEC patients. Four studies recruited exclusively female patients, while four others had the majority of their study population as female patients. Only one study reported the mean age of their population to be less than 50 years old. Ten studies only recruited patients who were chemotherapy-naïve (*Table 1*).

CR

The triple antiemetic regimen was not superior to other antiemetic therapies for CINV in the acute phase (OR =1.26, 95% CI: 0.97–1.64). Subgroup analyses of HEC and MEC studies also found a similar conclusion (*Figure 1A*).

The combination of NK_1RA, PALO and DEX was statistically superior to other regimens in the delayed phase (OR =1.26; 95% CI: 1.03–1.55). In HEC studies, the triplet was not statistically superior to other treatments, but the combination was better than other regimens in MEC studies (OR =1.57, 95% CI: 1.15–2.14) (*Figure 1B*). The RD between the intervention arms in MEC studies satisfied the MASCC/ESMO 10% threshold (*Table 2*).

With respect to the overall CR, NK_1RA, PALO and DEX were statistically superior to other regimens (OR =1.50, 95% CI: 1.26–1.78). Subgroup analyses revealed that the statistical difference prevailed among MEC (OR =1.82, 95% CI: 1.53–2.18) and HEC studies (OR =1.25, 95% CI: 1.01–1.55) (*Figure 1C*). RD among MEC studies surpassed the MASCC/ESMO guidelines, while the RD of all studies approaches the 10% requirement (*Table 2*).

Table 1 Characteristics of RCTs included in meta-analysis

Trial	Study Design	Intervention	Sample size	Chemotherapy emetogenicity	Females (%)	Mean age (years)	Nonusers of alcohol (%)	Chemotherapy-naïve (%)
Herrington *et al.* 2008 (20)	Randomized, double-blind, placebo-controlled comparative	(I) PALO + DEX + APR; (II) PALO + DEX	(I) 55; (II) 16	HEC	(I) 69.5; (II) 87.5	(I) 58.9; (II) 56.1	(I) 79.7; (II) 75.0	(I) 96.6; (II) 87.5
Navari *et al.* 2011 (21)	Randomized phase III	(I) APR + PALO + DEX; (II) OLN + PALO + DEX	(I) 120; (II) 121	HEC	(I) 31.0; (II) 33.0	(I) 61.0*; (II) 63.0*	(I) N/a; (II) N/A	(I) 100; (II) 100
Ozaki *et al.* 2013 (22)	Randomized phase III	(I) PALO + DEX; (II) APR + PALO + DEX	(I) 39; (II) 21	MEC	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) N/A; (II) N/A
Wenzell *et al.* 2013 (23)	Open-label, randomized, pilot	(I) PALO + DEX + APR; (II) ODN + DEX + APR	(I) 20; (II) 20	HEC	(I) 100; (II) 100	(I) 50.9; (II) 52.9	(I) N/A; (II) N/A	(I) N/A; (II) N/A
Aapro *et al.* 2014 (24)	Randomized, double-blind phase III	(I) NEPA (NETU + PALO) + DEX; (II) PALO + DEX	(I) 724; (II) 725	MEC	(I) 98.2; (II) 97.9	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) 100; (II) 100
Hesketh *et al.* 2014 (25)	Double-blind, double-dummy, parallel	(I) PALO + DEX or APR + OND + DEX; (II) NETU + PALO + DEX	(I) 270; (II) 409	HEC	(I) 42.6; (II) 42.8	(I) N/A; (II) N/A	(I) 58.1; (II) 57.2	(I) 100; (II) 100
Fujiwara *et al.* 2015 (26)	Randomized, non-blinded, crossover comparative	(I) PALO + APR + DEX; (II) GRAN+ APR + DEX	(I) 38; (II) 38	HEC	(I) 100; (II) 100	(I) 57.5; (II) 57.5	(I) N/A; (II) N/A	(I) N/A; (II) N/A
Kaushal *et al.* 2015 (27)	Randomized	(I) PALO + DEX + APR; (II) ODN + DEX	(I) 30; (II) 30	MEC	(I) 3.3; (II) 23.3	(I) 52.0*; (II) 51.0*	(I) N/A; (II) N/A	(I) 100; (II) 100
Kimura *et al.* 2015 (28)	Randomized, single-blind, crossover	(I) PALO + DEX + APR; (II) GRAN + DEX + APR	(I) 12; (II) 12	HEC	(I) 41.7; (II) 58.3	(I) 36.1; (II) 50.6	(I) N/A; (II) N/A	(I) N/A; (II) N/A
Kusagaya *et al.* 2015 (29)	Open-label, parallel-group, randomized	(I) PALO + DEX + APR; (II) PALO + DEX	(I) 41; (II) 39	MEC	(I) 29.3; (II) 28.2	(I) 70.0*; (II) 73.0*	(I) 61.0; (II) 71.8	(I) 100; (II) 100
Matsumoto *et al.* 2015 (30)	Randomized double-blind active-controlled	(I) PALO + DEX + FOS; (II) GRAN + DEX + FOS	(I) 163; (II) 163	HEC	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) 100; (II) 100
Babu *et al.* 2016 (31)	Randomized pilot	(I) APR + PALO + DEX; (II) OLN + PALO + DEX	(I) 50; (II) 50	HEC	(I) 70.0; (II) 70.0	(I) 44.7; (II) 43.3	(I) N/A; (II) N/A	(I) 100; (II) 100
Ruhlmann *et al.* 2016 (32)	Randomized, double-blind, placebo-controlled, phase 3	(I) FOS + DEX + PALO; (II) DEX + PALO	(I) 118; (II) 116	HEC	(I) 100; (II) 100	(I) 48.0*; (II) 47.0*	(I) N/A; (II) N/A	(I) 100; (II) 100
Suzuki *et al.* 2016 (33)	Randomized, double-blind, phase III	(I) PALO + DEX + APR; (II) GRAN + DEX + APR	(I) 414; (II) 413	HEC	(I) 25.8; (II) 25.2	(I) 63.0*; (II) 64.0*	(I) N/A; (II) N/A	(I) N/A; (II) N/A

Table 1 *(continued)*

Table 1 *(continued)*

Trial	Study Design	Intervention	Sample size	Chemotherapy emetogenicity	Females (%)	Mean age (years)	Nonusers of alcohol (%)	Chemotherapy-naïve (%)
Aapro *et al.* 2017 (34)	Randomized, double-blind phase III	(I) NEPA (NETU + PALO) + DEX; (II) PALO + DEX	(I) 724; (II) 725	MEC	(I) 98.3; (II) 98.0	(I) 54.0*; (II) 54.0*	(I) 80.9; (II) 81.3	(I) 100; (II) 100
Ogata *et al.* 2017 (35)	Randomized	(I) PALO + DEX + APR; (II) GRAN + DEX + APR	(I) 246; (II) 245	HEC	(I) 100; (I) 100	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) N/A; (II) N/A
Zhang *et al.* 2017 (36)	Randomized, double-blind, phase 3	(I) NEPA (NETU + PALO) + DEX; (II) APR + GRAN + DEX	(I) 412; (II) 416	HEC	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) N/A; (II) N/A	(I) 100; (II) 100

*, median age. APR, aprepitant; DEX, dexamethasone; FOS, fosaprepitant; GRAN, granisetron; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; N/A, data not available or extractable; NETU, netupitant; ODN, odansetron; OLN, olanzapine; PALO, palonosetron.

CC

There was no difference in CC between the combination and other intervention arms in the acute phase (OR =1.11, 95% CI: 0.90–1.36) (*Figure 2A*). The combination was superior to the other antiemetic regimens in the delayed (OR =1.40; 95% CI: 1.20–1.64) (*Figure 2B*) and the overall (OR =1.32, 95% CI: 1.14–1.54) phases (*Figure 2C*). These observations were mirrored in the subgroup analyses by emetogenicity. None of the RD values approached the MASCC/ESMO requirement for consideration of revision of guidelines (*Table 2*).

No nausea

NK_1RA, PALO and DEX was not superior to other treatments in the acute phase in controlling nausea (OR =1.36, 95% CI: 0.98–1.87). Similarly, there was no difference between the treatment arms in the HEC and MEC settings (*Figure 3A*). In the delayed phase, there was also no difference in nausea control (OR =0.90; 95% CI: 0.52–1.55). This finding was also similar in the HEC and population (*Figure 3B*).

The triplet was not statistically similar to other treatments in the overall phase (OR =1.18; 95% CI: 0.90–1.55), and also in the HEC setting (OR =0.88; 95% CI: 0.37–2.11) (*Figure 3C*). RD analysis indicates that the difference noticed in MEC studies is not considerably large to be studied by MASCC/ESMO anti-emetics panel (*Table 2*).

No emesis

NK_1RA, PALO and DEX was superior to the other therapies in the acute phase (OR =1.47, 95% CI: 1.11–1.95) (*Figure 4A*). There was also no difference between the two arms in the delayed phase (OR =1.47, 95% CI: 0.82–2.64) (*Figure 4B*). The RD for the acute and delayed phases did not pass the 10% MASCC/ESMO requirement (*Table 2*).

With respect to the overall phase, NK_1RA, PALO and DEX was superior (OR =1.69, 95% CI: 1.34–2.14). It was also superior in both the MEC setting (OR =1.86, 95% CI: 1.56–2.22) (*Figure 4C*). Only RD of MEC studies surpassed the MASCC/ESMO requirement (*Table 2*).

Discussion

This is the first study to our knowledge that compared the efficacy of the triple-drug antiemetic regimen recommended

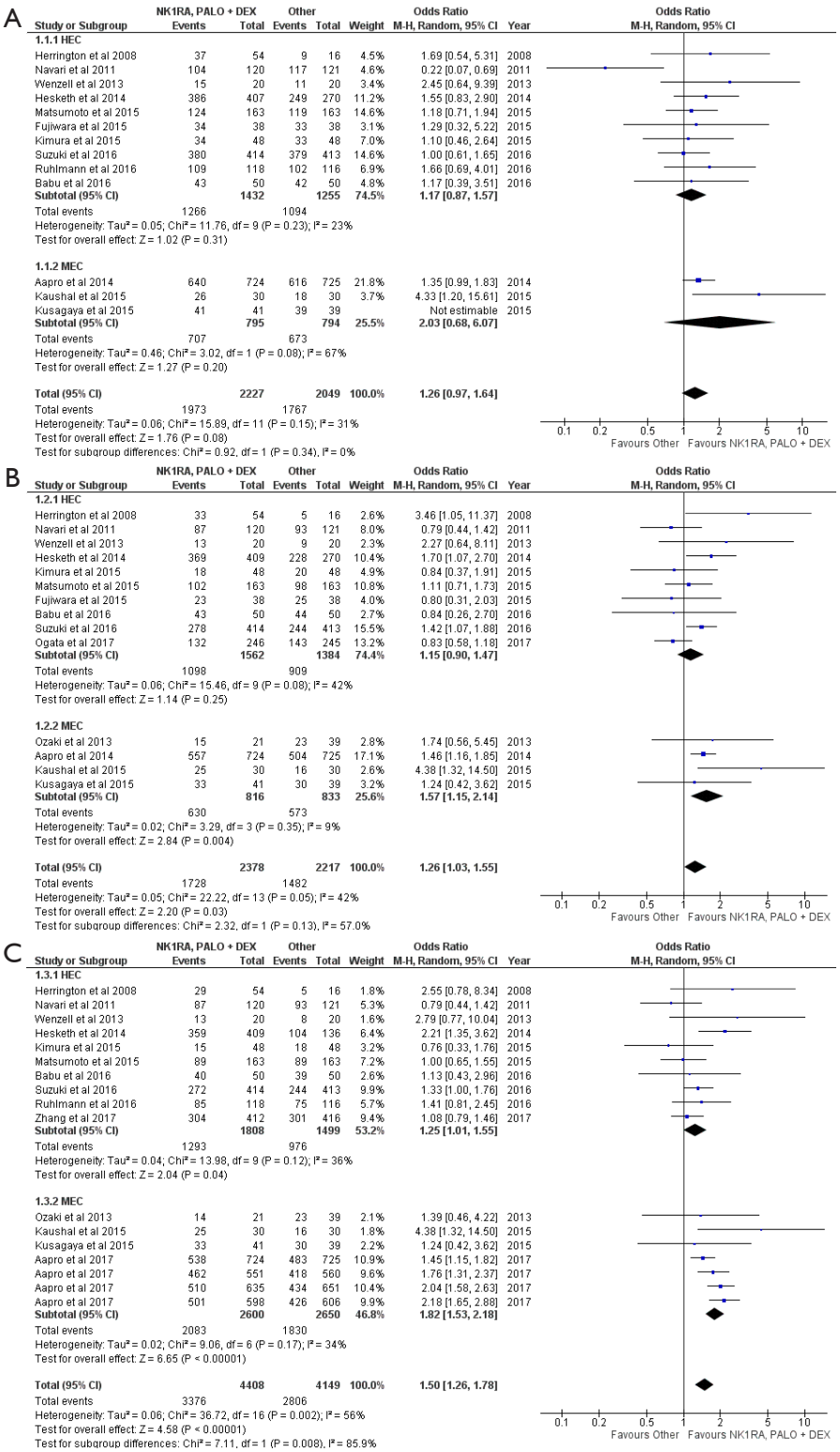

Figure 1 Efficacy of NK_1, palonosetron and dexamethasone compared with others in the prophylaxis of chemotherapy-induced nausea and vomiting—CR. (A) Acute phase; (B) delayed phase; (C) overall phase. NK1RA, neurokinin-1 receptor antagonist; CR, complete response; PALO, palonosetron; DEX, dexamethasone; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

Table 2 Absolute RD between NK1 receptor antagonist, palonosetron and dexamethasone versus other intervention arms for all included chemotherapy-induced nausea and vomiting endpoints

Endpoint	Absolute RD (%)	95% CI (%)	Test for overall effect (P value)	Heterogeneity test (P value)	Satisfies MASCC/ESMO antiemetic guidelines requirement
CR, acute phase	2	–1 to 4	0.29	0.03	No
HEC	1	–3 to 4	0.65	0.11	No
MEC	4	–3 to 11	0.26	0.03	No
CR, delayed phase	4	0 to 8	0.03	0.05	No
HEC	3	–2 to 7	0.28	0.09	No
MEC	10	2 to 18	0.02	0.24	Yes
CR, overall phase	8	5 to 11	<0.00001	0.01	Approaching requirement
HEC	4	0 to 9	0.03	0.18	No
MEC	11	8 to 14	<0.00001	0.22	Yes
CC, acute phase	1	–1 to 4	0.31	0.82	No
HEC	1	–2 to 4	0.41	0.63	No
MEC	1	–3 to 5	0.55	N/A	No
CC, delayed phase	7	4 to 10	<0.0001	0.79	No
HEC	7	3 to 11	0.002	0.58	No
MEC	7	2 to 12	0.006	N/A	No
CC, overall phase	6	3 to 9	0.0004	0.82	No
HEC	6	2 to 10	0.007	0.62	No
MEC	6	1 to 11	0.02	N/A	No
No nausea, acute phase	3	1 to 7	0.21	0.34	No
HEC	2	–1 to 5	0.26	0.70	No
MEC	23	–1 to 48	0.06	N/A	Yes
No nausea, delayed phase	–3	–13 to 8	0.64	<0.00001	No
HEC	–10	–23 to 3	0.14	<0.0001	Yes
MEC	18	–8 43	0.17	0.03	Yes
No nausea, overall phase	3	–3 to 8	0.29	<0.00001	No
HEC	–3	–21 to 14	0.69	<0.00001	No
MEC	6	3 to 8	<0.00001	0.55	No
No emesis, acute phase	3	1 to 5	0.002	0.95	No
HEC	3	0 to 6	0.03	0.90	No
MEC	4	0 to 7	0.03	N/A	No
No emesis, delayed phase	4	–3 to 11	0.23	0.001	No
HEC	5	–5 to 15	0.36	0.0010	No
MEC	6	2 to 10	0.004	N/A	No
No emesis, overall phase	7	4 to 11	<0.00001	0.007	No
HEC	5	–1 to 11	0.11	0.04	No
MEC	10	7 to 12	<0.00001	0.43	Yes

CC, complete control; CR, complete response; ESMO, European Society of Medical Oncology; MASCC, Multinational Association of Supportive Care in Cancer; N/A, not applicable; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy; RD, risk difference.

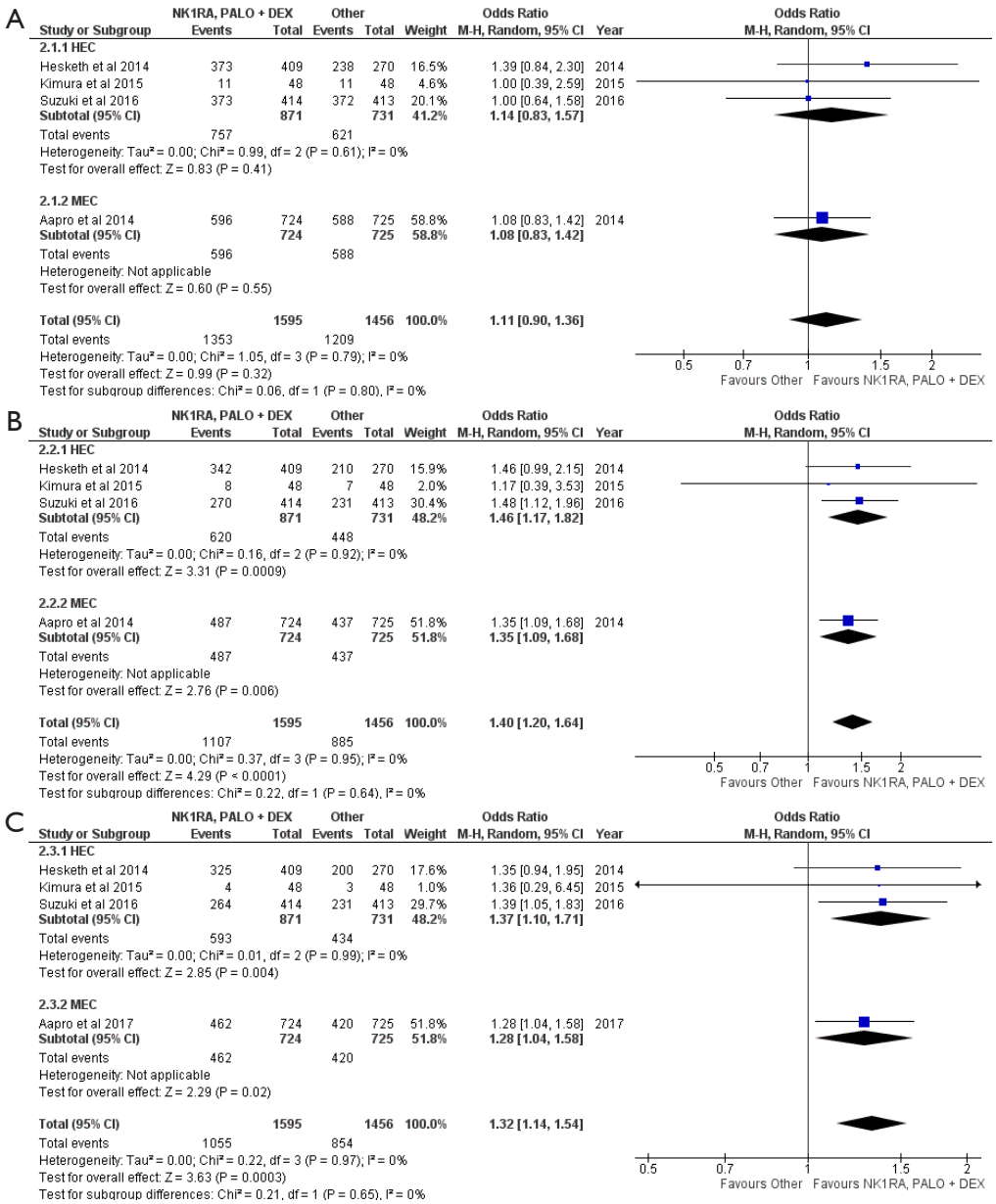

Figure 2 Efficacy of NK_1RA, palonosetron and dexamethasone compared with others in the prophylaxis of chemotherapy-induced nausea and vomiting—CC. (A) Acute phase; (B) delayed phase; (C) overall phase. NK1RA, neurokinin-1 receptor antagonist; CR, complete response; PALO, palonosetron; DEX, dexamethasone; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

by MASCC/ESMO (for treatment of CINV in the HEC setting) with any other treatments, as reported in RCTs. Our analyses indicate that the combination is superior to other treatments in all but six endpoints—CC, CR and nausea in the acute phase, nausea and emesis control in the delayed phase, and nausea in the overall phase. However, in almost all of the phase III studies, studies measured nausea as a secondary endpoint and employed different case-definitions.

More importantly, when looking only at HEC and MEC studies, the combination was only superior to others (i.e., 5-HT_3RA and DEX; other 5-HT_3RA other than

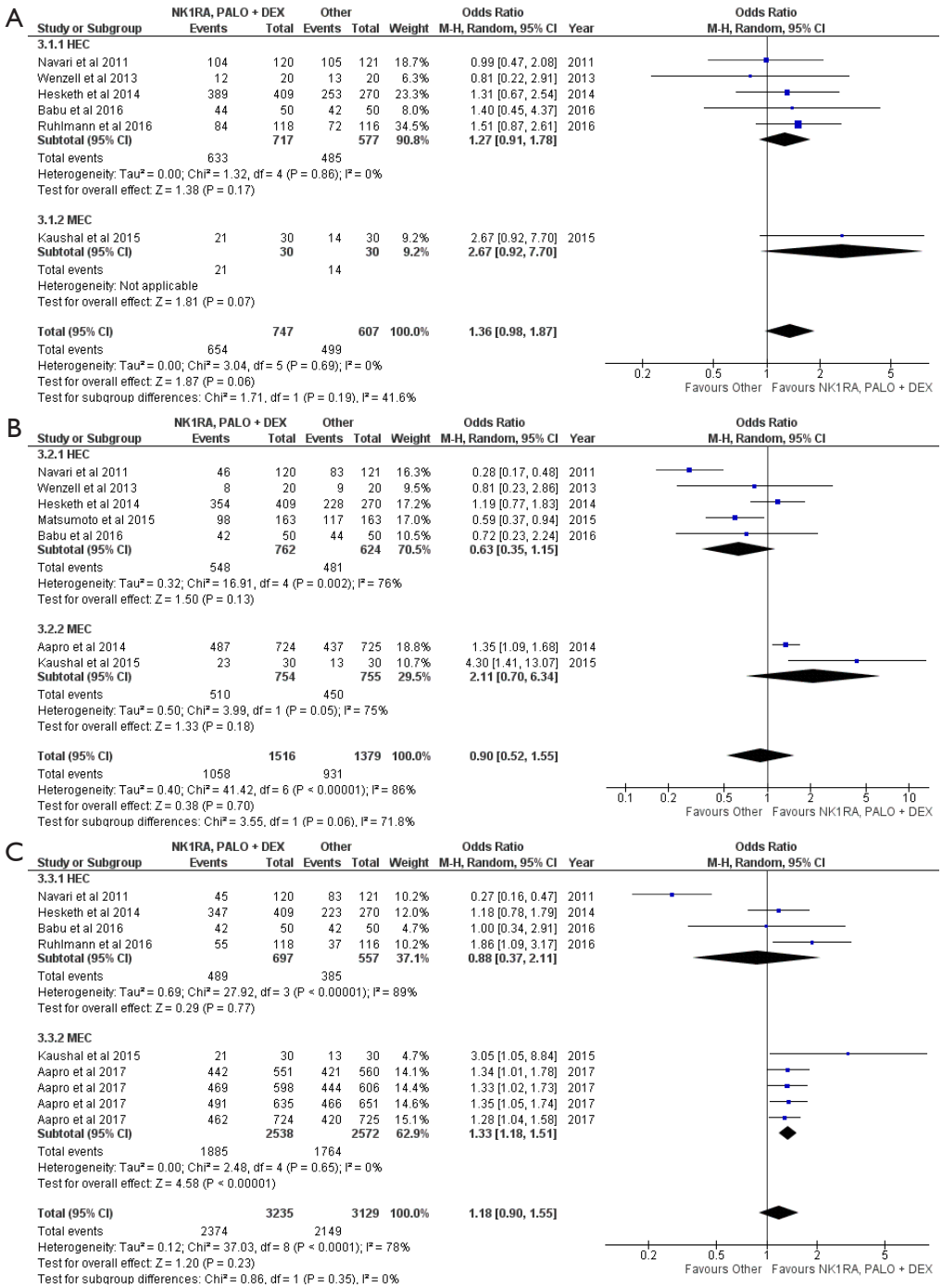

Figure 3 Efficacy of NK_1RA palonosetron and dexamethasone compared with others in the prophylaxis of chemotherapy-induced nausea and vomiting—no nausea. (A) Acute phase; (B) delayed phase; (C) overall phase. NK1RA, neurokinin-1 receptor antagonist; CR, complete response; PALO, palonosetron; DEX, dexamethasone; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

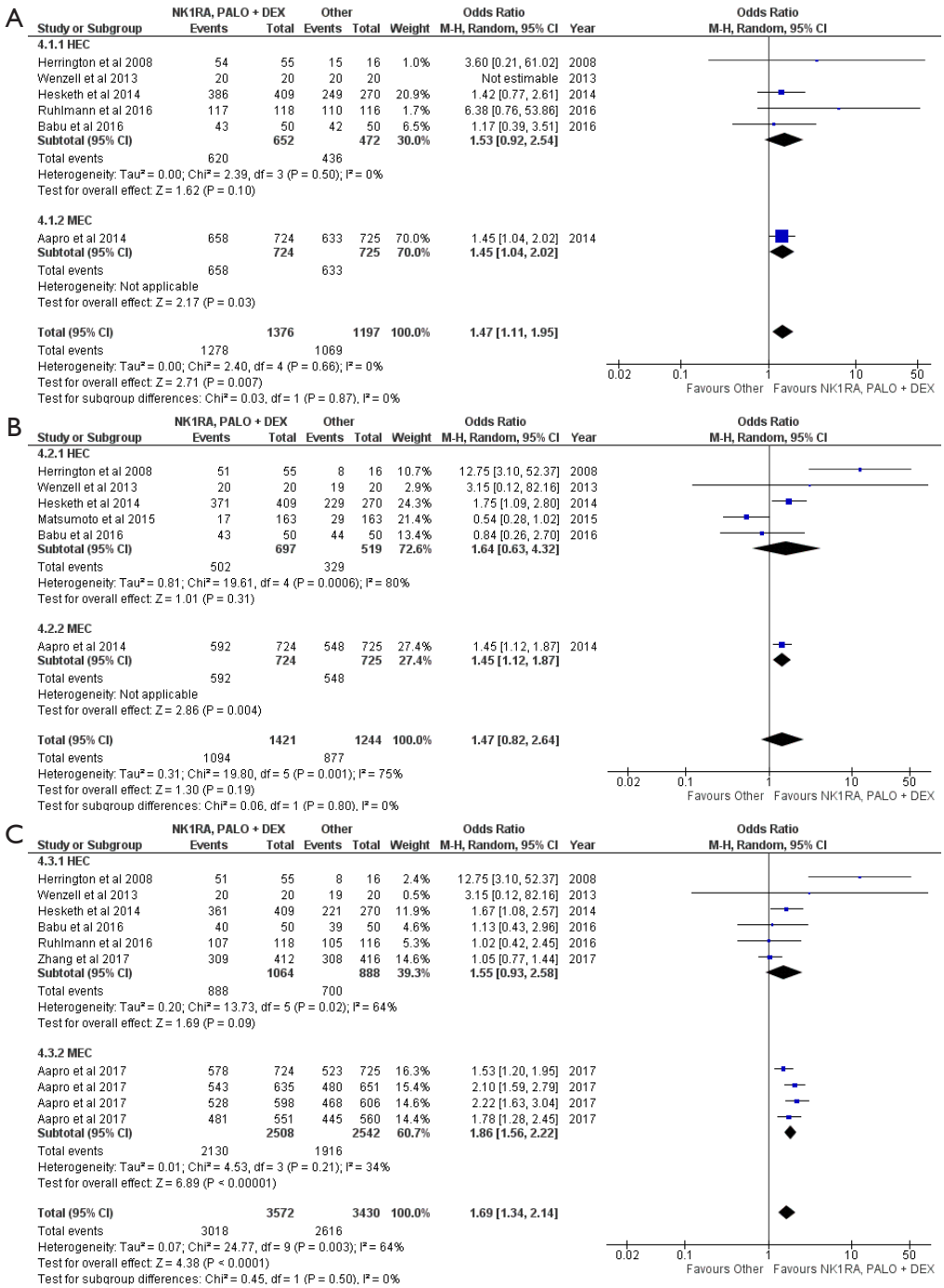

Figure 4 Efficacy of NK_1RA palonosetron and dexamethasone compared with others in the prophylaxis of chemotherapy-induced nausea and vomiting—no nausea. (A) Acute phase; (B) delayed phase; (C) overall phase. NK1RA, neurokinin-1 receptor antagonist; CR, complete response; PALO, palonosetron; DEX, dexamethasone; HEC, highly emetogenic chemotherapy; MEC, moderately emetogenic chemotherapy.

PALO with DEX and NK_1RA) in three endpoints (overall CR, delayed CC and overall CC) in the HEC setting, which is less than the nine identified endpoints (delayed and overall CR, delayed and overall CC, overall nausea control, and acute, delayed and overall phases for emesis control) in the MEC setting. This observation may be a result of HEC studies simply substituting other $5\text{-}HT_3RAs$ in the other treatment arms such as granisetron (GRAN) (23,29,31,34) and ondansetron (24,35), while MEC studies generally completely omitted a class of RAs, such as a NK_1RA (20,21,27,28,32), in the comparison arm. The lack of NK_1RA, when interpreted in lieu of the fact that the triple-combination arm is more efficacious in the delayed setting for CR, CC, no nausea and no emesis, supports the data that the difference between HEC and MEC studies are a result of the different comparison arms (presence of NK_1RA).

The studies of MEC patients that compared a triple antiemetic regimen with a two-antiemetic regimen indicate that the triplet is more efficacious. RD analysis suggests that the combination should be further investigated by the MASCC/ESMO antiemetic guideline panel on the basis that four of the 12 endpoints surpass the 10% threshold. However, not many of our included RCTs documented safety endpoints that could be analyzed using the Mantel-Haenszel method, and more study needs to investigate the safety endpoints for consideration of the panel. Nevertheless, ASCO, NCCN and MASCC/ESMO should investigate into recommending the triple regimen in the MEC setting (adding a NK_1RA to the antiemetic regimen), as the results suggest that it is superior to the currently-recommended double-drug regimen.

There are limitations of the present meta-analysis. An inherent limitation of all included RCTs was that differential outcomes between arms for the acute phase may carry-over and affect the results of delayed phase endpoints (37). These endpoints could be explored further in a more controlled setting where antiemetic outcomes on day 1 do not interfere with delayed endpoints. Additionally, some studies were only available for data extraction in abstract form (22,30,35,36). Attempts were made to reach out to authors to see if they could provide more data, not all authors responded.

Conclusions

In conclusion, the combination of NK_1RA, PALO and DEX is not inferior to other antiemetic regimens; in fact, the triplet was suggested to be superior in the majority of assessed endpoints. Among MEC patients, in particular, the triple-regimen was suggested to be more efficacious than other regimens that omit NK_1RA. Further studies should investigate into the safety of the triple regimen compared to regimens lacking NK_1RA, to add to the discussions about whether future CINV prophylaxis guidelines should include NK_1RA as a first-line treatment in the MEC setting in addition to the already-suggested HEC setting.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Search strategy

Search strategy

Database: Ovid MEDLINE(R) (1946 to June Week 4 2017)

1. exp Neoplasms/ and chemotherap*.mp. [320223]
2. exp Neoplasms/dt [437300]
3. exp Antineoplastic agents/ [970314]
4. exp Antineoplastic combined chemotherapy protocols/ [128474]
5. or/1-4 [1196069]
6. Nausea/ [15061]
7. Vomiting/ [22140]
8. (nausea or vomiting).mp. [84508]
9. or/6-8 [84508]
10. (Palonosetron or ALOXI).mp. [416]
11. (comparative or compar* or comparison or combin* or alone).mp. [6192288]
12. exp Neurokinin-1 Receptor Antagonists/ [1906]
13. ("neurokinin 1 receptor antagonist" or "NK1R antagonist" or "NK1 antagonist").mp. [610]
14. (aprepitant or Emend or casopitant or Rezonic or Zunrisa or ezlopitant or netupitant or Akynzeo or vestipitant).mp. [963]
15. 10 and (11 or 12 or 13 or 14) [338]
16. 5 and 9 and 15 [258]
17. limit 16 to (English language and humans) [231]
18. limit 17 to clinical trial, all [100]

Database: Embase Classic + Embase (1947 to 2017 Week 27)

1. exp cancer chemotherapy/ [331594]
2. exp neoplasm/dt (Drug Therapy) [583938]
3. exp neoplasm/ and chemotherap*.mp. [541891]
4. exp antineoplastic agent/ [1924484]
5. or/1-4 [2186361]
6. exp "nausea and vomiting"/ [301251]
7. (nausea or vomiting).mp. [326675]
8. "chemotherapy induced nausea and vomiting"/ [2561]
9. 6 or 7 or 8 [330281]
10. palonosetron/ or (palonosetron or ALOXI).mp. [1686]
11. exp comparative study/ or (comparative or compar* or comparison or combin* or alone).mp. [8797012]
12. exp neurokinin 1 receptor antagonist/ [2155]
13. ("neurokinin 1 receptor antagonist" or "NK1R antagonist" or "NK1 antagonist").mp. [2682]
14. aprepitant/ or Emend.mp. [2875]
15. casopitant/ or (Rezonic or Zunrisa).mp. [173]
16. ezlopitant/ [104]
17. netupitant plus palonosetron/ or netupitant/ or Akynzeo.mp. [219]
18. vestipitant/ [67]
19. 10 and (or/11-18) [1410]
20. (8 or (5 and 9)) and 19 [1077]
21. limit 20 to (human and English language) [958]
22. limit 21 to (RCT or controlled clinical trial) [128]
23. clinical trial/ and (randomised or randomized).mp. [336589]
24. (21 and 23) or 22 [138]

EBM reviews—Cochrane Central Register of Controlled Trials (May 2017)

1. (exp Neoplasms/ or (neoplasm* or cancer).mp.) and chemotherap*.mp. [33583]
2. exp Neoplasms/dt [9805]
3. exp Antineoplastic agents/ [37895]
4. exp Antineoplastic combined chemotherapy protocols/ [11626]
5. or/1-4 [58426]
6. Nausea/ [3024]
7. Vomiting/ [2693]
8. (nausea or vomiting).mp. [34211]
9. or/6-8 [34211]
10. (Palonosetron or ALOXI).mp. [292]
11. (comparative or compar* or comparison or combin* or alone).mp. [556402]
12. exp Neurokinin-1 Receptor Antagonists/ [100]
13. ("neurokinin 1 receptor antagonist" or "NK1R antagonist" or "NK1 antagonist").mp. [138]
14. (aprepitant or Emend or casopitant or Rezonic or Zunrisa or ezlopitant or netupitant or Akynzeo or vestipitant).mp. [334]
15. 10 and (11 or 12 or 13 or 14) [247]
16. 5 and 9 and 15 [139]
17. limit 16 to English language [121]

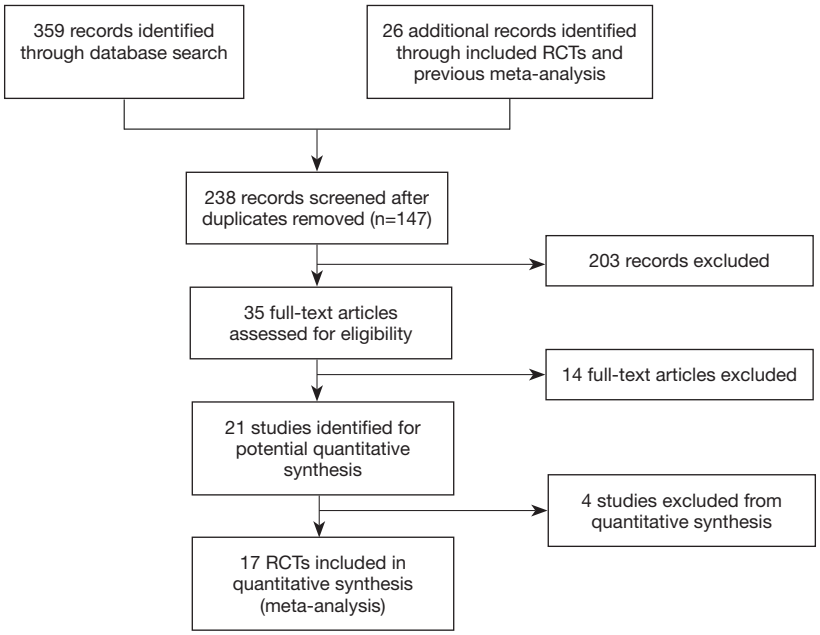

Figure S1 PRISMA flow diagram. RCT, randomized controlled trial.