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REVIEW

Neurokinin-1 Receptor Antagonists for Chemotherapy-Induced Nausea and Vomiting: A Systematic Review

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Background The addition of neurokinin-1 receptor (NK1R) antagonists to antiemetic regimens has substantially reduced chemotherapy-induced nausea and vomiting (CINV). We sought to systematically review the overall impact of NK1R antagonists on CINV prevention.

Methods We systematically searched the MEDLINE, EMBASE, and CENTRAL databases, and meeting proceedings for randomized controlled trials (RCTs) that evaluated NK1R antagonists plus standard antiemetic therapy for CINV prevention. Complete response (CR) to therapy was defined as the absence of emesis and the absence of rescue therapy. The endpoints were defined as CR in the overall phase (during the first 120 hours of chemotherapy), CR in the acute phase (first 24 hours), and the delayed phase (24–120 hours) after chemotherapy, nausea, and toxicity. Subgroup analyses evaluated the type of NK1R antagonist used, the emetogenic potential of the chemotherapy regimen, and prolonged use of 5-HT3 (serotonin) receptor antagonists, a class of standard antiemetic agents. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using a random-effects model. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates and publication bias were two-sided.

Results Seventeen trials (8740 patients) were included in this analysis. NK1R antagonists increased the CR rate in the overall phase from 54% to 72% (OR = 0.51, 95% CI = 0.46 to 0.57, $P < .001$). CR and nausea were improved in all phases and subgroups. The expected side effects from NK1R antagonists did not statistically significantly differ from previous reports; however, this analysis suggests that the incidence of severe infection increased from 2% to 6% in the NK1R antagonist group (three RCTs with a total of 1480 patients; OR = 3.10; 95% CI = 1.69 to 5.67, $P < .001$).

Conclusions NK1R antagonists increased CINV control in the acute, delayed, and overall phases. They are effective for both moderately and highly emetogenic chemotherapy regimens. Their use might be associated with increased infection rates; however, additional appraisal of specific data from RCTs is needed.

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Nausea and vomiting are common and feared symptoms among cancer patients (1–3), and up to 80% of patients will experience chemotherapy-induced nausea and vomiting (CINV) without prophylactic therapy (1–5). Nausea and vomiting can lead to deteriorated nutritional status, compromise adherence to therapy, and impair quality of life irrespective of etiology. Furthermore, inadequate emesis control may lead to anticipatory nausea and vomiting, which is a challenging clinical condition to treat and potentially refractory to standard medications (6,7).

The intrinsic risk of the chemotherapy regimen is the main risk factor for the overall degree of CINV and can vary depending on the class of drug, dose, schedule, and route of administration used. The current classification of the risk of emesis is mostly based on the intrinsic emetogenic potential of the chemotherapy regimen (8–10), which is stratified as follows: high emetogenic potential (>90% risk of inducing vomiting after chemotherapy administration), moderate emetogenic potential (>30–90% risk), low emetogenic potential (10–30% risk), and minimal emetogenic potential (<10% risk) (8).

Patient characteristics such as young age, female sex, low alcohol intake, poor performance status, previous history of bowel obstruction, history of motion sickness, and experience of emesis during pregnancy (11–13) may further increase the emetic risk but are currently not factors that are integrated into the choice of optimal prophylactic therapy. Additionally, disease-related features such as the primary site of the cancer, the histological subtype, clinical stage, presence of brain metastases, and presence of end organ dysfunction may further impact the probability of emesis. The use

of adjunct therapies such opioid derivatives, radiotherapy, or other medications can also exacerbate symptoms. Although the stratification usually applied to evaluate emetic risk does not consider important and relevant clinical and disease factors, it is accepted worldwide.

Cisplatin is the main example of a drug with a high emetogenic potential; doses greater than 50 mg/m² lead to nausea and vomiting in more than 90% of patients if no prophylactic therapy is used (8). Other drugs with high emetogenic potential include cyclohosphamide (>1500 mg/m²), carmustine (>250 mg/m²), and dacarbazine.

Efforts to prevent and treat CINV have been usually directed at blocking neurotransmitter receptors in the area postrema, which is a chemoreceptor trigger site for vomiting in response to emetic drugs. Dopamine, endorphin, serotonin, and neurokinin receptors are found in this area and are targets for preventing and treating CINV (14). Although the combination of dexamethasone and serotonin (5-HT3) receptor antagonists remained the backbone of CINV prevention until recently, this combination has been reported to lack effectiveness in preventing late onset CINV (15–20).

More than a decade ago, Navari et al. (21) showed that neurokinin-1 receptor (NK1R) antagonists improve CINV when used in combination with cisplatin-based chemotherapy (21). These antagonists prevent the binding of substance P to the NK1R. Unopposed, substance P, a tachykinin family neuropeptide that functions as a neurotransmitter and neuromodulator, can mediate the induction of vomiting pathways by binding to the NK1R (22).

Current guidelines for CINV management (11,13,23) strongly recommend the use of NK1R antagonists for CINV prophylaxis in the acute and delayed phases for highly emetogenic chemotherapy schedules. We planned this systematic review with meta-analysis to evaluate the overall effectiveness and safety of NK1R antagonists in the prevention of CINV and have reported it according to Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (24).

Methods

Search Strategy

To evaluate the effectiveness and safety of NK1R antagonists in preventing CINV, we searched for randomized controlled trials (RCTs) that compared the addition of NK1R antagonists to standard antiemetic regimens, including a 5-HT3 antagonist plus dexamethasone, for cancer patients receiving chemotherapy, regardless of its emetogenic potential. We performed an electronic database search of MEDLINE (last search, December 21, 2010), EMBASE (last search, September 30, 2010), the Cochrane Central Register of Controlled Trials—CENTRAL (last search, September 26, 2010), and LILACS (last search, August 1, 2010), and, electronically or manually, we searched all conference proceedings of the American Society of Clinical Oncology (ASCO), the American Society of Hematology (ASH) and the European Society for Medical Oncology (ESMO) between 1998 and 2010. We used a wide search strategy for the electronic database with the following combinations of keywords: neurokinin, aprepitant, casopitant, ezlopitant, netupitant, vestipitant (and their respective codes), chemotherapy-induced nausea and vomiting, nausea in cancer patients, vomiting in cancer patients, and randomized trials (25). The reference lists of all recovered trials and relevant reviews were also considered. Sources with the most recent data were used whenever possible. Language and publication date restrictions were not applied.

Selection Criteria

Two reviewers (LVS, FHS) screened titles and abstracts identified from the search strategy for eligibility. Both reviewers independently selected trials for inclusion according to prior agreement regarding the study population and intervention. The studies of interest were RCTs that addressed the addition of an NK1R antagonist to standard antiemetic therapy (dexamethasone plus 5-HT3 antagonist) for the prevention of CINV. Studies were eligible for inclusion in our analysis if they provided an adequate description of outcomes that could be pooled in the meta-analysis and used adequate antiemetic therapy in the control arm (dual therapy). If one of the reviewers determined that an abstract was eligible, the full text version was retrieved and selected upon concordance between LVS and FHS. Full text versions of all eligible studies were obtained for quality assessment and data extraction.

Quality Assessment and Data Extraction

Two reviewers (LVS, FHS) independently assessed the quality of each study using the full text article, and two reviewers (JPL, LVS) independently performed the data extraction. The data extraction form (available upon request) included the following items: general information (authors, title, journal, date of publication, protocol name, and duplication of publication), methodological characteristics of the RCTs (method of randomization, allocation concealment, blinding, drop-out description, calculation of the sample size, intention-to-treat principle, funding source), study population (number of patients, types of cancer, age), chemotherapy emetogenic potential and outcomes (26,27). Any disagreement was discussed until all three reviewers reached consensus. The characteristics directly related to the risk of bias were analyzed in subgroups to test their impact on the estimation of the effect size.

Outcomes of Interest

The primary outcome that we tabulated was the proportion of patients who achieved a complete response (CR) during the overall period of assessment (ie, during the acute and delayed phases after chemotherapy; 0–24 hours and 24–120 hours, respectively). CR was defined as the absence of vomiting or retching and the absence of the need for rescue antiemetic drugs. CR in the acute and delayed phases was a secondary outcome. Symptoms that appeared within the first 24 hours after administration of chemotherapy were classified as acute and those that appeared from 24 to 120 hours after the administration of chemotherapy were considered as delayed. Other secondary outcomes were nausea and vomiting during the acute, delayed, and overall periods. Nausea was classified according to a 100-mm visual analogical scale (VAS), where 0 mm correlates to absence of nausea and 100 mm correlates to the worst possible nausea experienced by the patient. In this classification, patients with a visual analogical scale less than 5 mm were classified as having "no nausea," and patients with a visual analogical scale less than 25 mm were classified as having "no (clinically) significant nausea." Reported adverse events were also a secondary outcome.

Statistical Analysis and Synthesis

RevMan 5.0 software was used to perform the meta-analysis (28). The Mantel–Haenszel random-effects method was used to calculate odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) (29). We measured the occurrence of events such that an OR less than 1 favored the NK1R antagonist group in the primary and secondary endpoints. The number needed to treat—or the number needed to harm in case of toxicity—to benefit one single patient was calculated as 1/[experimental event rate – control event rate].

The statistical heterogeneity of trial results was assessed by the χ^2 test and expressed as I^2 plus the corresponding P value. Heterogeneity was considered substantial if I^2 was 50% or greater (29,30) and, if encountered, a plausible explanation was intensively pursued. If a reasonable cause for heterogeneity between trials was found, a separate analysis was then performed to explore the impact of this factor on the estimation of the effect size. If the cause was not apparent and if heterogeneity was generated by divergent data (ie, data favoring one or other treatment), the data would then not be pooled.

Publication bias was evaluated by Egger's test using Comprehensive Meta-Analysis software, version 2.0 (31–33). The estimation for the impact of publication bias was done using the "Trim and Fill" method (34). This method consists in representing the "missing" (or unpublished) studies in a funnel plot graph and then calculating the impact these studies would have in the estimation of the effect size.

If a given study had more than one interventional arm, we chose to combine all intervention groups to avoid multiple counting of the same individuals in the control arm (so called unit-of-analysis error) (35). For example, if a trial had two interventional arms (with different doses of NK1R antagonists) and one control arm (with no NK1R antagonists), the number of subjects and events in both interventional arms was added and then compared with the number of subjects and events in the control arm for each endpoint.

Predefined subgroup analyses were undertaken in clinically relevant subsets to evaluate the impact of these subgroups on the estimation of the effect size. The following comparisons were carried out: chemotherapy emetogenic potential (highly vs moderately emetogenic chemotherapy), NK1R antagonist treatment length (1 day vs more than 1 day), route of administration (oral vs intravenous vs both), the characteristics of the control group (presence vs absence of 5-HT3 antagonist instead of placebo, in the control group only, during the delayed phase), type of drug (aprepitant vs casopitant vs other), and dexamethasone dose modification because of pharmacological interaction with the NK1R antagonist. Sensitivity analyses based on methodological quality parameters were performed to test for possible variations in estimates of ORs between subgroups.

Additional exploratory analyses using Spearman's rank correlation coefficient (r_s) were performed to test for potential correlations between responses in the acute and delayed phases. Statistical tests for heterogeneity were one-sided; statistical tests for effect estimates and publication bias were two-sided.

Results

Description of Studies

Four-thousand and thirty-four studies were retrieved by electronic and manual search methods. Forty-two articles were selected and closely scrutinized for eligibility, and 19 of them were excluded because of duplication. The remaining 23 studies met the inclusion criteria and were selected for analysis (21,36–57). Six studies were further excluded for the following reasons: Herrington et al. (43) prematurely terminated the placebo control group because of unacceptable emesis events and did not provide data from this interim analysis; Yeo et al. (53) included patients who had already been enrolled in a previously published study included in this meta-analysis (52), and therefore this study was excluded to avoid double-counting; Bubalo et al. (56) did not provide extractable data; Shumway et al. (54) was excluded because of the absence of dual therapy in the control arm; and Van Belle et al. (51) and Cocquyt et al. (39) had not used a 5-HT3 receptor antagonist in the experimental arms.

Seventeen studies (21,36–38,40–42,44–50,52,55,57) were eligible for quantitative synthesis and analysis, comprising 8740 patients (Figure 1). Sixteen were fully published, whereas one study was only available as a meeting abstract (55). The main methodological characteristics of the selected trials are summarized (Table 1).

We extracted data from only one of the experimental arms in the de Wit et al. study because the other experimental arm with higher doses of NK1R antagonist was prematurely terminated in light of new pharmacokinetic data (40). Patients enrolled in the Chawla et al. study came from a second randomization procedure started in de Wit et al. study (38,40). Because no patients were double-counted as described by Chawla et al., we extracted and pooled data from these two studies separately. Moreover, two of four arms from the Campos et al. study were excluded because of the absence of a 5-HT3 antagonist in the experimental arms (37).

All studies were reported in English (21,36–38,40–42,44–50,52,55,57), and all but one were multicentered (55). Only three studies used intention-to-treat analysis (36,41,49); however, the drop-out rate for the remaining studies was less than 5% (21,37,38,40,42,44–48,50,52,55,57). Three studies used ondansetron, an active antiemetic agent, in place of a placebo in the control arm from day 2 to the last day of therapy (48,50,52). Nine studies decreased the dexamethasone dose in the experimental arm in an attempt to prevent pharmacokinetic interaction with NK1R antagonists (41,42,46–50,52,57). All studies were blinded.

There were no major divergences in the definition of outcomes among the selected studies. Oral and intravenous casopitant preparations were analyzed irrespective of their administration route. The Roila et al. study showed data for five experimental arms (casopitant in four and aprepitant in one); in order to avoid unit-of-analysis error, these arms were grouped as "other NK1R antagonists" (49). The antiemetic regimens of the selected studies are summarized in Table 2.

Complete Response and Other Efficacy Outcomes

Data from 8173 patients in 13 studies were available for CR in the overall phase. The frequency of vomiting, retching, or use of rescue medication was statistically significantly decreased among patients who received NK1R antagonists compared with the standard therapy (OR = 0.51, 95% CI = 0.46 to 0.57, $P < .001$). In the experimental arm, 3759 of 5252 patients (72%) had a complete response in the overall phase, whereas only 1569 of 2921 (54%) patients in the control arm did ($P < .001$) (Figure 2). Among patients given aprepitant, 1459 of 2268 (64.3%) had a CR vs 977 of 1972 (49.5%)

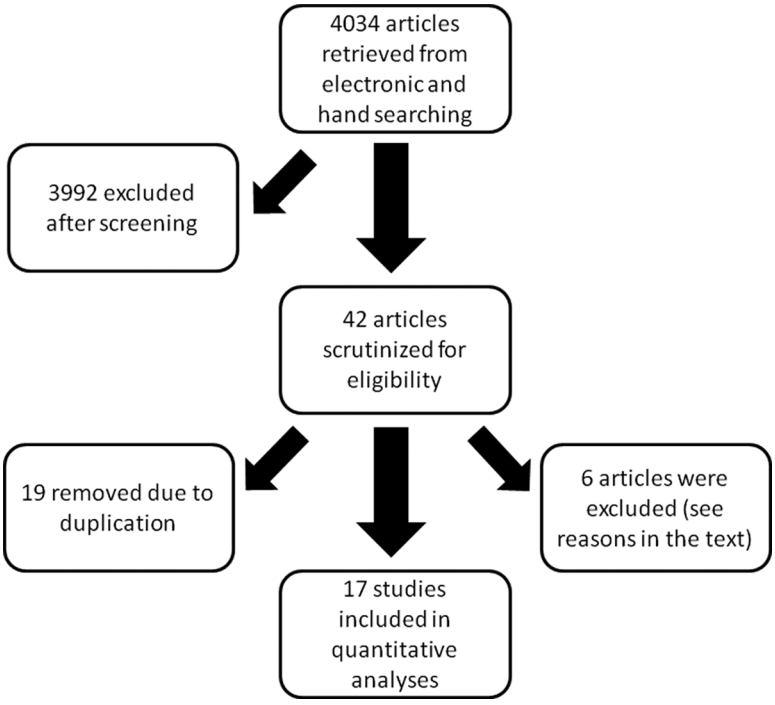

Figure 1. Flow chart of search strategy and study selection.

Table 1. Main methodological characteristics of included studies

Trial	No. of patients	Randomization method and allocation concealment	Blinding/ placebo controlled	Drop-out description	ITT*	Funding	Predetermined alpha-error and power	Reference
Navari (1999)	159	Adequate	Yes	Yes	No	Unclear†	Yes	(21)
Hesketh (1999)	61	Unclear	Yes	Yes	No	Pharm Company only	Yes	(45)
Campos (2001)	351	Adequate	Yes	Yes	No	Pharm Company plus other sources	Yes	(37)
Chawla (2003)	381	Adequate	Yes	Yes	No	Pharm Company only	Yes	(38)
de Wit (2003)	202	Adequate	Yes	Yes	No	Pharm Company only	Yes	(40)
Hesketh (2003)	530	Adequate	Yes	Yes	No	Pharm Company only	Yes	(46)
Poli-Bigelli (2003)	569	Adequate	Yes	Yes	No	Pharm Company only	Yes	(47)
Warr (2005)	866	Adequate	Yes‡	Yes	No	Pharm Company only	Yes	(52)
Schmoll (2006)	489	Adequate	Yes‡	Yes	No	Pharm Company only	Yes	(50)
Joshi (2007)	36	Unclear	Yes	No	No	Unclear	No	(55)
Arpornwirat (2009)	723	Adequate	Yes	Yes	Yes	Pharm Company only	Yes	(36)
Gore (2009)	46	Unclear	Yes	Yes	Yes	Pharm Company only	No	(41)
Grunberg 2009	810	Adequate	Yes	Yes	No	Pharm Company only	Yes	(42)
Herrstedt (2009)	1933	Adequate	Yes	Yes	No	Pharm Company only	Yes	(44)
Roila (2009)	493	Adequate	Yes	Yes	Yes	Pharm Company only	Yes	(49)
Rapoport (2010)	848	Adequate	Yes‡	Yes	No	Pharm Company only	Yes	(48)
Takahashi (2010)	453	Adequate	Yes	Yes	No	Pharm Company only	Yes	(57)

* All studies that excluded patients from efficacy analysis after randomization were not considered as intention-to-treat (ITT) studies. Chawla (38) and De Wit (40) double-counted some patients, and two arms of Campos et al. (37) were excluded, so the total number of subjects in these studies was 8950 and the number of subjects analyzed in the meta-analysis was 8740.

† This study was probably funded by a pharmaceutical company.

‡ Active agent control in the delayed phase.

in the control arm. Among patients given casopitant, 1985 of 2575 (77.1%) had a CR vs 542 of 865 (62.6%) in the control arm.

For the acute phase, data from 8376 patients in 15 studies were included in the meta-analysis, and there was a statistically significant greater frequency of CR among patients who received NK1R antagonists compared with patients who did not receive them (OR = 0.56, 95% CI = 0.48 to 0.65, $P < .001$; Figure 3, A). Furthermore, data from 8375 patients in the same 15 studies were included in this meta-analysis for the evaluation of CR in the delayed phase. As expected, there was again a statistically significantly greater frequency of CR among patients who received NK1R antagonists (OR = 0.48, 95% CI = 0.42 to 0.56, $P < .001$; Figure 3, B).

For all other secondary outcomes—rate of emesis, no nausea, and no substantial nausea in all phases—the addition of a NK1R antagonist was superior to the control arm. However, in three

Table 2. Antiemetic regimens included in the selected studies*

Trial	N	D1	D2	D3	D4	D5	Emetogenic potential
Navari (1999)	159						High
	51	D 20 mg (IV) + Gr 10 μg/kg (IV)					
	54	D 20 mg (IV) + Gr 10 μg/kg (IV) + A 400 mg	A 300 mg	A 300 mg	A 300 mg	A 300 mg	
	54	D 20 mg (IV) + Gr 10 μg/kg (IV) + A 400 mg					
Hesketh (1999)	61						High
	31	D 20 mg + Gr 10 μg/kg					
	30	D 20 mg + Gr 10 μg/kg + Ez 100 mg bid	Ez 100 mg bid	Ez 100 mg bid	Ez 100 mg bid	Ez 100 mg bid	
Campos (2001)	351						High
	90	D 20 mg + Gr 10 μg/kg (IV)					
	86	D 20 mg + Gr 10 μg/kg (IV) + A 400 mg	A 300 mg	A 300 mg	A 300 mg	A 300 mg	
Chawla (2003)†	381						High
	127	D 20 mg + O 32 mg (IV)	D 8 mg	D 8 mg	D 8 mg	D 8 mg	
	134	D 20 mg + O 32 mg (IV) + A 125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	
	120	D 20 mg + O 32 mg (IV) + A 40 mg	D 8 mg + A 25 mg	D 8 mg + A 25 mg	D 8 mg + A 25 mg	D 8 mg + A 25 mg	
de Wit (2003)‡	202						High
	86	D 20 mg + O 32 mg (IV)	D 8 mg	D 8 mg	D 8 mg	D 8 mg	
	81	D 20 mg + O 32 mg (IV) + A 125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	
Hesketh (2003)	530						High
	266	D 20 mg + O 32 mg (IV)	D 8 mg bid	D 8 mg bid	D 8 mg bid		
	264	D 20 mg + O 32 mg (IV) + A 125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg		
Poli-Bigelli (2003)	569						High
	286	D 20 mg + O 32 mg (IV)	D 8 mg bid	D 8 mg bid	D 8 mg bid		
	283	D 20 mg + O 32 mg (IV) + A 125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg		
Warr (2005)	866						Moderate
	428	D 20 mg + O 8 mg	A 80 mg	A 80 mg			
	438	D 20 mg + O 8 mg + A 125 mg	O 8 mg bid	O 8 mg bid			
Schmoll (2006)	489						High
	245	D 20 mg + O 32 mg (IV)	D 8 mg bid + O 8 mg bid	D 8 mg bid + O 8 mg bid	D 8 mg bid + O 8 mg bid		
	244	D 12 mg + O 32 mg (IV) + A 125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg		
Joshi (2007)§	36						High
	19	D 20 mg + O 32 mg	D 8 mg	D 8 mg	D 8 mg	D 8 mg	
	17	D 20 mg + O 32 mg + A125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg	D 8 mg	
Arpornwirat (2009)	723						Moderate
	121	D 8 mg (IV) + O 8 mg bid	O 8 mg bid	O 8 mg bid			
	120	D 8 mg (IV) + O 8 mg bid + C 50 mg	O 8 mg bid + C 50 mg	O 8 mg bid + C 50 mg			
	121	D 8 mg (IV) + O 8 mg bid + C 100 mg	O 8 mg bid + C 100 mg	O 8 mg bid + C 100 mg			
	120	D 8 mg (IV) + O 8 mg bid + C 150 mg	O 8 mg bid + C 150 mg	O 8 mg bid + C 150 mg			
	120	D 8 mg (IV) + O 8 mg bid + C 150 mg	O 8 mg bid	O 8 mg bid			
	121	D 8 mg (IV) + O 16 mg + C 150 mg	O 16 mg + C 150 mg	O 16 mg + C 150 mg			
Gore (2009)‖	46						Unknown
	18	D 16 mg + O 0.15 mg/kg (IV) tid	D 8 mg + O 15 mg/kg (IV) tid	D 8 mg	D 8 mg		
	28	D 8 mg + O 0.15 mg/kg (IV) tid + A 125 mg	D 4 mg + O 15 mg/kg (IV) tid + A 80 mg	D 4 mg + A 80 mg	D 4 mg		

(Table continues)

Table 2. (Continued)

Trial	N	D1	D2	D3	D4	D5	Emetogenic potential
Grunberg 2009	810						High
	269	D 20 mg + O 32 mg (IV)	D 8 mg bid	D 8 mg bid	D 8 mg bid		
	271	D 12 mg + O 32 mg (IV) + C 150 mg	D 8 mg bid	D 8 mg bid	D 8 mg bid		
	270	D 12 mg + O 32 mg (IV) + C 90 mg (IV)	D 8 mg + C 50 mg	D 8 mg + C 50 mg	D 8 mg		
Herrstedt 2009	1933						Moderate
	483	D 8 mg (IV) + O 8 mg bid	O 8 mg bid	O 8 mg bid			
	483	D 8 mg (IV) + O 8 mg bid + C 150 mg	O 8 mg bid	O 8 mg bid			
	483	D 8 mg (IV) + O 8 mg bid + C 90 mg (IV)	O 8 mg bid + C 50 mg	O 8 mg bid + C 50 mg			
	484	D 8 mg (IV) + O 8 mg bid + C 150 mg	O 8 mg bid + C 50 mg	O 8 mg bid + C 50 mg			
Roila 2009	493						High
	84	D 20 mg + O 32 mg (IV)	D 8 mg bid	D 8 mg bid	D 8 mg bid		
	82	D 12 mg + O 32 mg (IV) + C 50 mg	D 8 mg + C 50 mg	D 8 mg + C 50 mg	D 8 mg		
	81	D 12 mg + O 32 mg (IV) + C 100 mg	D 8 mg + C 100 mg	D 8 mg + C 100 mg	D 8 mg		
	81	D 12 mg + O 32 mg (IV) + C 150 mg	D 8 mg + C 150 mg	D 8 mg + C 150 mg	D 8 mg		
	83	D 12 mg + O 32 mg (IV) + C 150 mg	D 8 mg bid	D 8 mg bid	D 8 mg bid		
	82	D 12 mg + O 32 mg (IV) + A 125 mg	D 8 mg + A 80 mg	D 8 mg + A 80 mg	D 8 mg		
Rapoport 2010	848						Moderate
	418	D 20 mg + O 8 mg bid	O 8 mg bid	O 8 mg bid			
	430	D 20 mg + O 8 mg bid + A 125 mg	A 80 mg	A 80 mg			
Takahashi 2010	453						High
	151	D 6 mg (IV) + Gr 40 μg/kg (IV) + A 125 mg	D 4 mg (IV) + A 80 mg	D 4 mg (IV) + A 80 mg	A 80 mg	A 80 mg	
	151	D 8 mg (IV) + Gr 40 μg/kg (IV) + A 40 mg	D 6 mg (IV) + A 25 mg	D 6 mg (IV) + A 25 mg	A 25 mg	A 25 mg	
	151	D 12 mg (IV) + Gr 40 μg/kg (IV)	D 8 mg (IV)	D 8 mg (IV)			

* All interventions are oral and once daily, except those otherwise specified. A = aprepitant; C = casopitant; D = dexamethasone; Ez = ezlopitant; Gr = granisetron; IV = intravenous; O = ondansetron. Aprepitant, casopitan, and ezlopitant are neurokinin 1 receptor antagonists.

† There were two distinct randomizations in this study, and only the second randomization was analyzed. The first randomization was analyzed in de Wit et al.

‡ The high-dose experimental arm was interrupted before the end of the study.

§ Dexamethasone was extended until D7. This study was reported as an abstract form, and the route of administration for dexamethasone and ondansetron on D1 was unclear.

‖ Patients from 11 to 18 years of age.

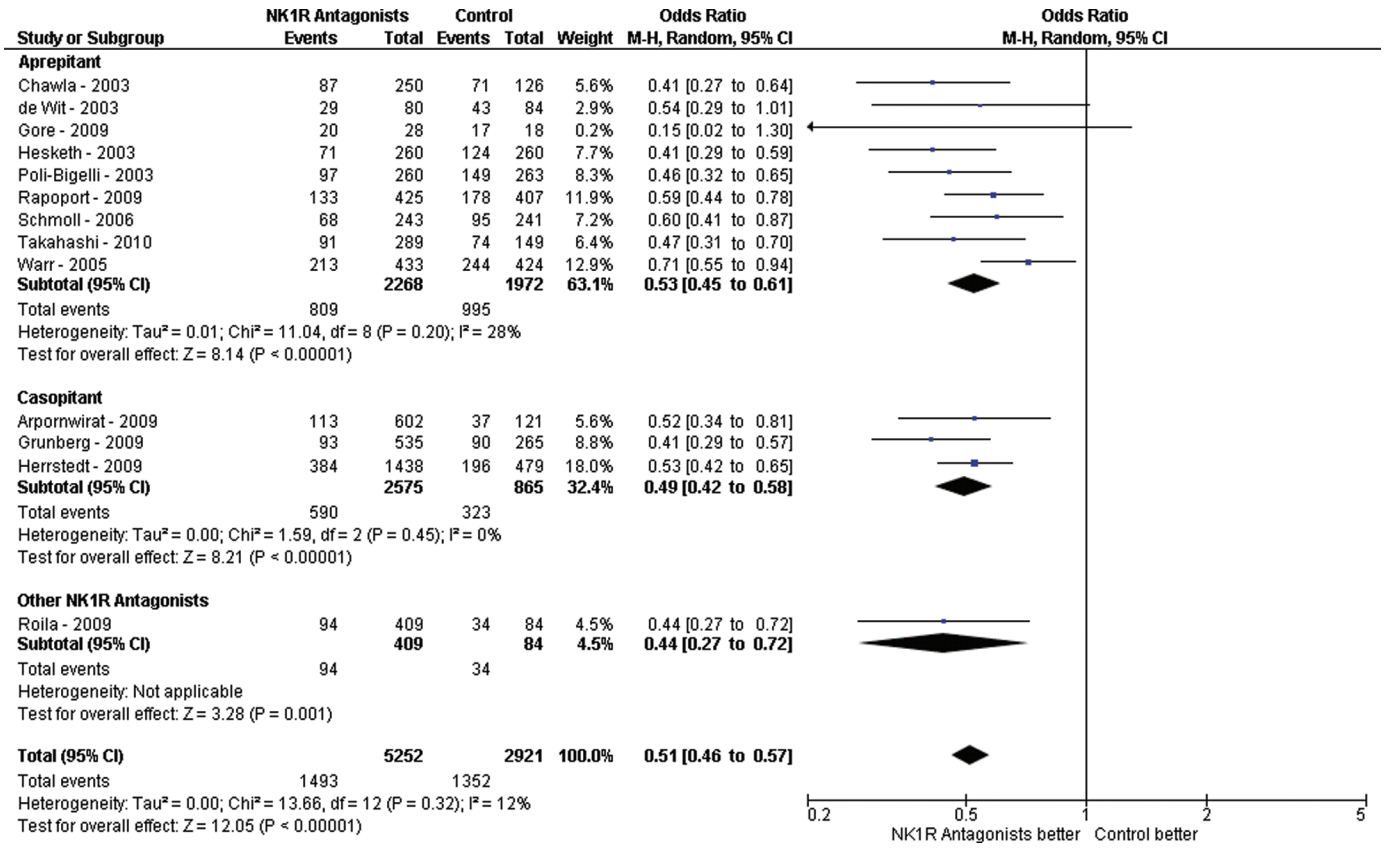

Figure 2. Forest plot of odds ratios for achieving an overall complete response (CR) to NK1R antagonists as antiemetic agents among patients undergoing chemotherapy. **Squares** denote the results of individual studies, whereas **diamonds** represent the estimation of the pooled effect size. The **horizontal lines** represent 95% confidence intervals.

secondary endpoints (no emesis in the delayed phase and no nausea in the acute and delayed phases), the effect size could not be estimated because of the heterogeneity seen among trials. We chose not to pool the data because we could not identify the reasons for such findings (Supplementary Table, available online).

Subgroup Analysis

The addition of a NK1R antagonist to standard antiemetic therapy improved CR rates in the overall phase for patients who received highly emetogenic chemotherapy (54%–73%, OR = 0.46, 95% CI = 0.40 to 0.53, $P < .001$) or moderately emetogenic chemotherapy (54%–71%, OR = 0.59, 95% CI = 0.51 to 0.67, $P < .001$), as defined in Table 2. Considering that the control arms for highly and moderately emetogenic chemotherapy were not dissimilar, the differences suggest that the addition of a NK1R antagonist yields a superior magnitude of impact favoring their use in highly emetogenic chemotherapy schedules ($P_{interaction} = .015$).

The addition of NK1R antagonists increased the CR rates in the overall phase independently if ondansetron was used in the control arm beyond day 1 (instead of placebo) (48,50,52) or not (21,36–38,40–42,44–47,49,55,57) (ondansetron use: 52%–62%, OR = 0.64, 95% CI = 0.54 to 0.76, $P < .001$; no ondansetron: 55%–74%, OR = 0.47, 95% CI = 0.41 to 0.53, $P < .001$); however, there is some suggestion that patients who did not use ondansetron had a greater benefit (interaction test: $P = .004$). As expected, NK1R antagonists enhanced the CR rates in the delayed period. The improvement was greater when compared with the use of a placebo, rather than ondansetron, beyond day 1 ($P_{interaction} < .001$). These findings suggest that 5-HT3 antagonists may help to prevent delayed CINV and may increase the success of overall CINV if added beyond day 1.

For all other subgroups (aprepitant vs casopitant, route of administration, dexamethasone dose adjustment, and NK1R antagonist therapy length), there was no evidence of statistically significant differences in treatment efficacy (data available upon request).

The study published by Roila et al. had six arms, four of them with casopitant and one with aprepitant (49). This allowed us a direct comparison of both drugs, and the results were not different from those obtained from indirect comparison in the subgroup analysis (CR in the overall phase—direct comparison, OR = 0.71, 95% CI = 0.41 to 1.23, $P = .22$).

Exploratory Analysis

We extracted the CR data for the acute and delayed phases for each arm from all 17 trials. The variables for each arm (acute vs delayed) were plotted in a scatter graph (Figure 4) that demonstrates a strong statistical correlation between CR in the acute phase and delayed phase, suggesting that the division of CINV in these intervals may be arbitrary ($r_s = 0.91$; two-tailed $P < .001$).

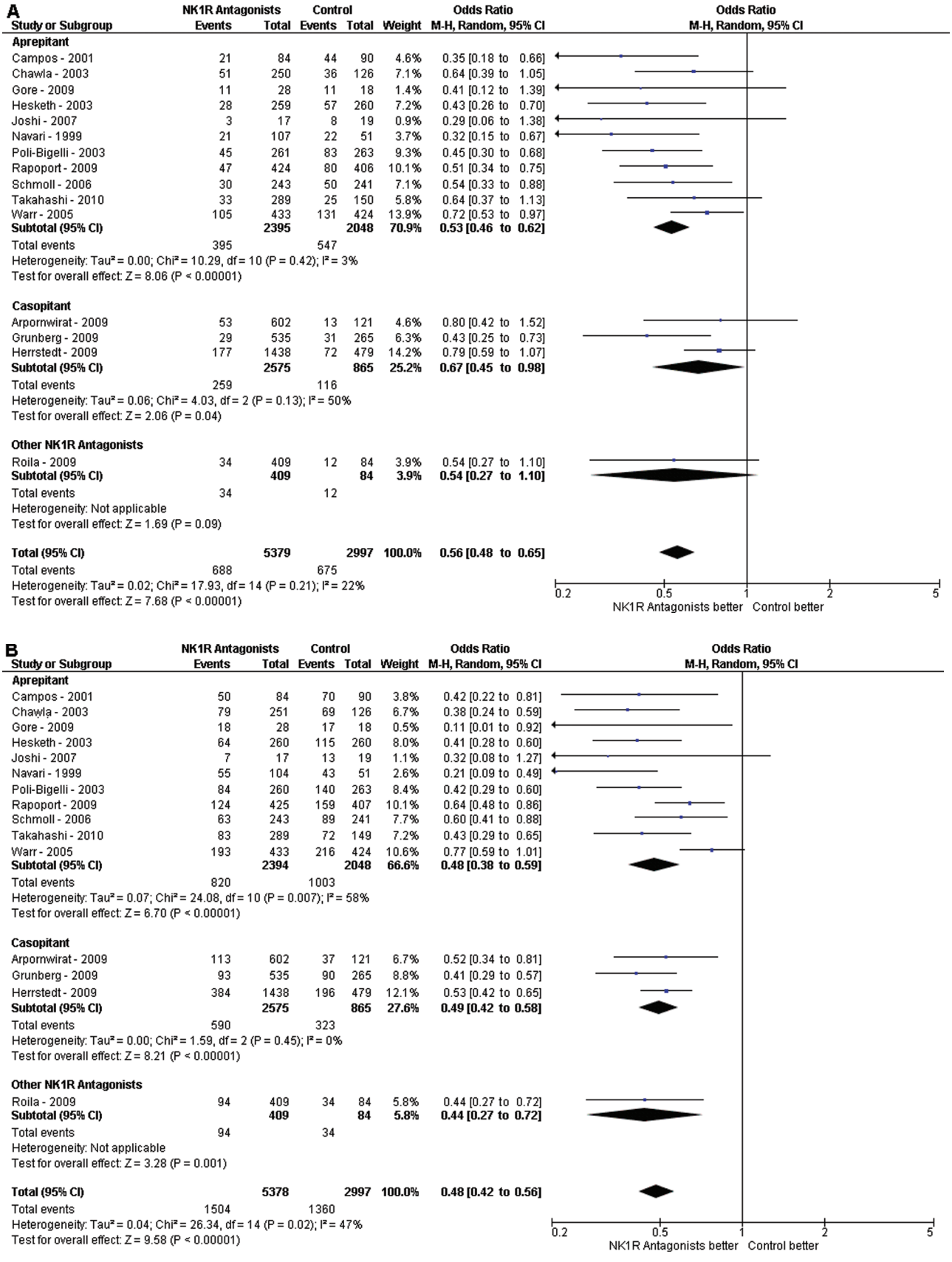

Figure 3. Forest plot of odds ratios for achieving a complete response (CR) to NK1R antagonists as antiemetic agents among patients undergoing chemotherapy at (**A**) the acute phase, 0–24 hours after administration of chemotherapy and (**B**) the delayed phase, 24–120 hours after administration of chemotherapy.

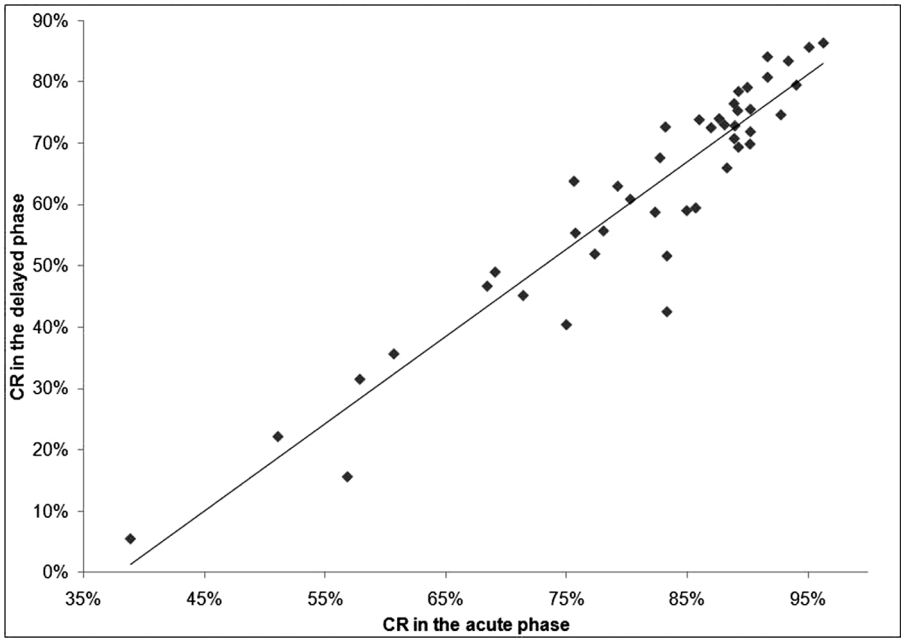

Figure 4. Correlation between a complete response (CR) and NK1R antagonists in the acute and delayed phases. CRs for both acute (0–24 hour) and delayed (24–120 hour) phases were plotted separately for each arm of included studies. There was a strong correlation between both variables (r_s = 0.91; two-tailed P < .001).

Toxicity

All 17 trials included in this meta-analysis reported safety data; however, the majority of trials limited the description to common expected toxicities with incidence in at least 10% of patients in each arm. Toxicity was described according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) in most studies.

The toxicity meta-analysis was restricted to events that occurred in the first cycle of chemotherapy because some trials used multiple cycles of chemotherapy but only one randomization procedure, and the drop-out patients among arms were not uniform; events that occurred in later cycles of chemotherapy in such cases were excluded (Table 3). Any grade hiccups (P = .03) and any grade fatigue/asthenia (P = .01) were more common among patients in the NK1R antagonist group, whereas any grade constipation (P < .001) was more common in the control group. However, use of NK1R antagonists was not associated with an increase in the risk of diarrhea.

Four trials included data regarding severe infections, as defined by CTCAE version 3.0, and pooling these trials led to considerable heterogeneity (I^2 =54%, P = .09). The source of heterogeneity was the Gore et al. study (41), which had some particular methodological issues that merit further consideration. It was a study with a small sample size (n = 46) that enrolled adolescent patients whose baseline characteristics were not sufficiently described. Furthermore, 12.5% of the patients who were given NK1R antagonists were not randomly assigned and came from an extended phase of the protocol. Hence, these characteristics justify our decision to exclude this trial from the severe infection analysis.

Three trials (38,47,50), including 1480 patients, were left for evaluation, which determined a statistically significant increase (from 2% to 6%) in the risk of severe infection among patients who received NK1R antagonists (OR = 3.10; 95% CI = 1.69 to 5.67, P < .001). Interestingly, NK1R antagonists did not increase patients' risk of febrile neutropenia or any other hematological toxicity.

The three aforementioned studies enrolled adult cancer patients whose primary diagnoses were mainly respiratory (41%), urogenital (29%), and head and neck cancers (7%) (38,47,50). These patients were assigned high-dose cisplatin therapy (>70 mg/m²). Only Chawla et al. (38) combined NK1R antagonists with a high dose of dexamethasone (20 mg) that is currently not used. Chawla et al. reported "serious infection-related adverse events" (affecting 28 of 214 [13%] patients in the NK1R antagonist group vs nine of 212 [4.2%] patients in the control group), Poli-Bigelli et al. (47) reported only the number of patients experiencing septic shock (three of 282 [1.0%] patients in the NK1R antagonist group vs two of 285 [0.7%] patients in the control group), and Schmoll et al. (50) reported the number of patients experiencing pneumonia (four of 243 [1.6%] patients vs two of 244 [0.8%] patients in the NK1R antagonist and control groups, respectively) and urinary tract infection (nine of 243 [3.7%] patients vs two of 244 [0.8%] patients in the NK1R antagonist and control groups, respectively). De Wit et al. (40) reported that 15 patients developed "infection-related serious adverse events" during the subsequent cycles (2–6), and only one of them came from the standard control arm, ie, 14 of 62 (22.5%) patients in the NK1R antagonist arm vs 1 of 60 (1.6%) in the control arm developed such adverse events. This information was not incorporated into the pooled data to preserve the advantages of randomization, but it clearly supports the overall findings that suggest an association between NK1R antagonists and severe infection. The timing of infection, the microbiological diagnosis, which chemotherapy regimens were prescribed, which patients developed severe infection, or any other specific details were not stated in the full text article of any study included in this systematic review.

Bias Analysis and Quality Assessment

There was no strong evidence of publication bias (Egger test: P = .09). All efficacy outcomes were corrected for publication bias

Table 3. Reported adverse events for all included studies*

Toxicity	No.	No. at risk (%)	OR (95%CI)†	*P*‡	I^2, %	NNH
Anemia		1513	0.97 (0.69 to1.37)	.87	3	NA
Control group	54	384 (14.1)				
NK1R group	157	1129 (13.9)				
Anorexia		4464	1.07 (0.89 to 1.29)	.45	0	NA
Control group	266	1784 (14.9)				
NK1R group	439	2680 (16.4)				
Asthenia or fatigue		7107	1.23 (1.05 to1.45)	.01	11	37
Control group	337	2510 (13.4)				
NK1R group	741	4597 (16.1)				
Constipation		8422	0.79 (0.69 to 0.90)	<.001	0	–38
Control group	506	3089 (16.4)				
NK1R group	734	5333 (13.8)				
Death		6074	1.11 (0.73 to 1.70)	.62	0	NA
Control group	40	2336 (1.7)				
NK1R group	59	3738 (1.6)				
Dehydration		2540	0.93 (0.41 to 2.11)	.85	40	NA
Control group	19	1109 (1.7)				
NK1R group	24	1431 (1.7)				
Diarrhea		3857	1.06 (0.87 to 1.30)	.56	0	NA
Control group	193	1589 (12.1)				
NK1R group	303	2268 (13.4)				
Dizziness		1748	1.41 (0.57 to 3.48)	.45	44	NA
Control group	26	505 (5.1)				
NK1R group	70	1243 (5.6)				
Headache		4155	0.84 (0.69 to 1.02)	.08	0	NA
Control group	209	1566 (13.3)				
NK1R group	300	2589 (11.6)				
Hiccups		2708	1.30 (1.03 to 1.64)	.03	0	24
Control group	144	1095 (13.2)				
NK1R group	279	1613 (17.3)				
Infection—severe§		1480	3.10 (1.69 to 5.67)	<.001	0	25
Control group	15	741 (2.0)				
NK1R group	44	739 (6.0)				
Febrile neutropenia		6940	1.11 (0.76 to 1.64)	.59	0	NA
Control group	43	2764 (1.6)				
NK1R group	81	4176 (1.9)				
Neutropenia, grade 3–4		3075	1.08 (0.56 to 2.08)	.82	6	NA
Control group	19	1373 (1.4)				
NK1R group	32	1703 (1.9)				
Neutropenia		5795	1.06 (0.83 to 1.34)	.66	29	NA
Control group	316	1870 (16.9)				
NK1R group	934	3925 (23.8)				
Leukopenia		3257	1.03 (0.82 to 1.30)	.78	5	NA
Control group	139	845 (16.4)				
NK1R group	387	2412 (16.0)				
Severe adverse events		6258	1.06 (0.81 to 1.99)	.69	36	NA
Control group	186	2499 (7.4)				
NK1R group	253	3759 (6.7)				

* N = number; OR = Odds Ratio; 95% CI = 95% confidence interval; NK1R = neurokinin 1 receptor; NNH = number needed to harm; NA = not applicable.

† An OR less than 1 favored the NK1R antagonist group, whereas an OR greater than 1 favored the control arm group.

‡ Odds Ratio (OR) and respective 95% CI were calculated using Mantel–Haenszel random-effects model. *P* values were from the estimation of effect size (and not from heterogeneity test). *P* values were two-sided.

§ The definition of severe infection used in this meta-analysis followed NCI-CTCAE v3.0 standardization.

using the "trim and fill" method, and no major impact on the effect size was found (Figure 5). The methodological characteristics of the selected trials included in this meta-analysis (described in Table 1) had no impact on the results obtained, as confirmed by a sensitivity analysis that we performed (these data are available upon request).

Discussion

This systematic review with meta-analysis compiles the best clinical evidence available regarding the use of NK1R antagonists for CINV prevention. As expected, NK1R antagonists improved CINV control in the overall, acute, and delayed phases after chemotherapy, confirming the results of individual RCTs. Overall, NK1R antagonists increased the control of vomiting or retching after chemotherapy by 18%, which can be translated to one additional patient free of vomiting (during the overall phase) for every six patients treated with a NK1R antagonist.

Individually, RCTs were unable to prove the efficacy of NK1R antagonists in preventing nausea, one of the most feared chemotherapy-related adverse events (58,59). We demonstrated in

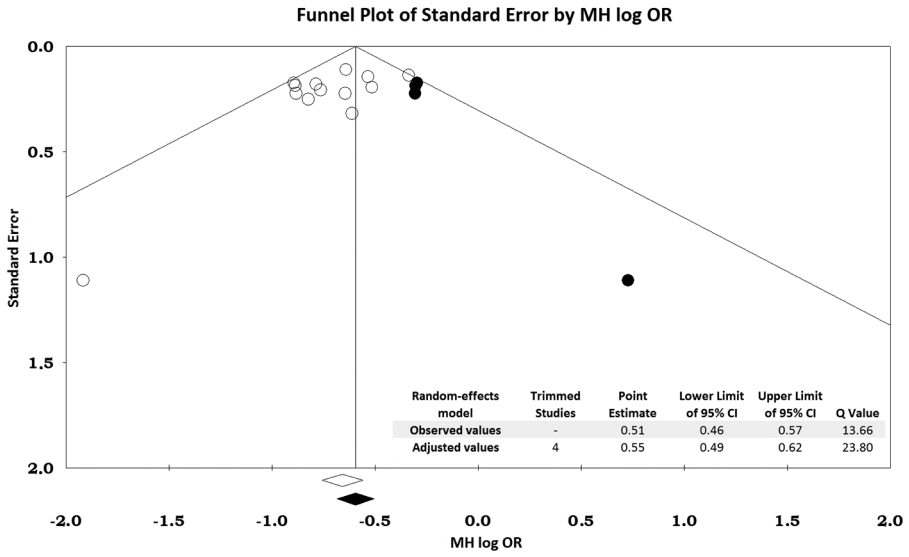

Figure 5. Funnel plot of standard error by Mantel–Haenszel (MH) log odds ratio (OR) for a complete response (CR) to NK1R antagonists in the overall phase. **White circles** represent individual studies; **white diamonds** represent the estimated combined effects. The two lines starting in the apex are the limits of standard error by MH log OR of the estimate of effect size. Duval and Tweedie's "trim and fill method" (34) was applied: the trimmed studies (**black circles**) caused a minor disturbance in the estimated effect size (**black diamonds**). Points estimated are Mantel–Haenszel OR and respective 95% confidence intervals (CI).

this meta-analysis that NK1R antagonists improved the frequency with which patients encountered no nausea or no substantial nausea, and such results should be considered new.

In addition, the present meta-analysis scrutinized particular scenarios and some interesting findings came to light. Our results demonstrate that cancer patients who receive moderately emetogenic chemotherapy derive an overall benefit from using NK1R antagonists, similar to patients who receive highly emetogenic chemotherapy, however, in lower magnitude. So far, NK1R antagonists have only been recommended in guidelines for cancer patients who receive highly emetogenic chemotherapy or anthracycline-cyclophosphamide schedules (11,13,23). Our results may suggest a reappraisal of their use in other chemotherapy regimens with lower emetic rates.

An interesting result is the apparently positive impact of prolonged ondansetron use in decreasing CINV in the delayed phase, an approach that is not supported by current guidelines (11,23) nor by a previously published systematic review with meta-analysis (60). Maybe the Geling and Eichler study (60) was underpowered to detect a benefit of prolonged ondansetron use. This finding was derived from a preplanned subgroup analysis and merits further evaluation considering its clinical relevance and the large availability of ondansetron worldwide.

Until this time, the ability of NK1R antagonists to mediate improvements in the acute phase after chemotherapy had not been correlated with their effectiveness in the delayed phase. We demonstrated a strong correlation (r_s =0.91) between controlling symptoms in the acute and delayed phases, irrespective of the use of a NK1R antagonist. This suggests that controlling emesis in the first 24 hours after chemotherapy administration may play a role in the prevention of delayed CINV.

An intriguing finding from the safety analyses is that the rate of severe infection was more frequent among patients who received NK1R antagonist therapy compared with the control group, with one more severe infections for every 25 patients treated. The definition of severe infection used in this meta-analysis followed NCI-CTCAE standardization. Respiratory and urinary tract infections were classified by CTCAE version 3 guidelines as at least grade 2 adverse events. These grade 2 events should be considered clinically important adverse events because they require, at least, interruption of chemotherapy until clinical recovery.

Only four of 17 studies described infection-related adverse events, and the severe infection analysis was derived from only three trials testing aprepitant in adult patients with cisplatin-based chemotherapy. In general, the authors restricted their reporting to the most prevalent adverse events (ie, those occurring in more than 10% of enrolled patients); this restriction limits the evaluation of low-frequency events and may potentially bias our findings.

NK1R antagonists are known to increase the bioavailability of dexamethasone (61), and this pharmacokinetic interaction could potentially play a role in the higher incidence of infection among patients who have been treated with NK1R antagonists. The Chawla et al. study (38) did not decrease the day 1 dexamethasone dose in the NK1R arm, whereas the Schmoll et al. (50) and Poli-Bigelli et al. (47) studies did. Nevertheless, it seems unlikely that increased dexamethasone bioavailability could have any impact on the infection rates because these three trials presented similar findings.

NK1R antagonists can also increase the bioavailability of chemotherapy agents metabolized by cytochrome P450 3A4 (CYP3A4), such as etoposide, taxanes, irinotecan, vinca alkaloids, anthracyclines, and cyclophosphamide. Two of three studies suggested that adverse events could be more common among patients receiving an NK1R antagonist plus a CYP3A4-metabolized chemotherapy (42,46,47). However, the increased risk of severe infection is probably not explained by hematological toxicity because leukopenia, neutropenia, severe neutropenia, and febrile neutropenia were not increased by the addition of NK1R antagonists.

Unfortunately, interactions with chemotherapy and other drugs could not be explored in this systematic review because of the absence of reporting of concomitant medications. Another

matter that might be considered is that the increased incidence of severe infection in NK1R antagonists group could be due to the immunomodulatory effects of this class of drugs. NK1R is known to have a role in neurogenic response to injury, and its suppression might impair natural defenses against infection (62–64) that might predispose patients to a greater risk of infection through immune-mediated mechanisms that are poorly understood.

We are aware that this study has the typical limitations of aggregate data meta-analysis; therefore, the findings and interpretations are limited by the quality and quantity of available data. Only presented or published data were used, and the existence of unpublished series should be considered; however, we found no indication of such bias. An individual-patient data meta-analysis could be more adequate for evaluating rare events (65), allowing the standardization of the type and grade of infection-related adverse events. The inclusion of more studies would enhance the power of such analysis, allowing a robust interpretation of these data.

In conclusion, NK1R antagonists, including aprepitant and casopitant, improved control of CINV in the acute, delayed, and overall phases for patients who received highly and moderately emetogenic chemotherapy. CINV control in the acute phase seemed to be a surrogate for CINV control in the delayed phase. The use of NK1R antagonists may be associated with a statistically significantly increased risk of severe infection. A more comprehensive evaluation of the safety profile of NK1R antagonists and additional appraisal of specific data from RCTs is needed.

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