

One-Day Versus Three-Day Dexamethasone with NK1RA for Patients Receiving Carboplatin and Moderate Emetogenic Chemotherapy: A Network Meta-analysis

Daichi Watanabe¹, Hirotohi Iihara^{1,*}, Hironori Fujii¹, Akitaka Makiyama², Shohei Nishida¹, Akio Suzuki¹

¹Department of Pharmacy, Gifu University Hospital, Gifu, Japan

²Cancer Center, Gifu University Hospital, Gifu, Japan

*Corresponding author: Hirotohi Iihara, PhD, Department of Pharmacy, Gifu University Hospital, Yanagido 1-1, Gifu 501-1194, Japan. Tel: 058-230-7088; Fax: 058-230-7084; Email: dai0920@gifu-u.ac.jp

Abstract

Background: The dexamethasone (DEX)-sparing strategy, which limits administration of DEX to day one, is reportedly non-inferior to conventional antiemetic regimens comprising multiple-day DEX. However, the usefulness of the DEX-sparing strategy in triplet antiemetic prophylaxis (neurokinin-1 receptor antagonist [NK1RA] + serotonin receptor antagonist [5HT3RA] + DEX) for carboplatin and moderate emetogenic chemotherapy (MEC) has not been clarified.

Patients and Methods: We systematically reviewed randomized controlled trials that examined the efficacy of antiemetics for preventing chemotherapy-induced nausea and vomiting associated with carboplatin and MEC. We conducted a network meta-analysis to compare the antiemesis efficacy of three-day DEX with NK1RA (3-DEX + NK1RA) and one-day DEX with NK1RA (1-DEX + NK1RA). The primary outcome was complete response during the delayed phase (CR-DP). The secondary outcome was no nausea during the delayed phase (NN-DP).

Results: Seventeen trials involving 4534 patients were included. The proportion who experienced CR-DP was 82.5% (95% credible interval [CrI], 73.9-88.6) and 73.5% (95% CrI, 62.8-80.9) among those who received 3-DEX + NK1RA and 1-DEX + NK1RA, respectively. There was no significant difference between the two regimens. However, 3-DEX + NK1RA tended to be superior to 1-DEX + NK1RA, with an absolute risk difference of 9.0% (95% CrI, -2.3 to 21.1) in CR-DP and 24.7% (95% CrI: -14.9 to 54.6) in NN-DP. 3-DEX + NK1RA also tended to be superior to 1-DEX + NK1RA in patients who received carboplatin-based chemotherapy, for whom the absolute risk difference was 12.3% (95% CrI, -3.2 to 30.7).

Conclusions: Care is needed when administering the DEX-sparing strategy in combination with NK1RA to patients receiving carboplatin and non-carboplatin MEC.

Key words: antiemetics; neurokinin-1 receptor antagonists; dexamethasone; nausea; vomiting; antineoplastic agents; carboplatin; network meta-analysis.

Implications for Practice

This study demonstrated that a three-day dose of dexamethasone (DEX) with neurokinin-1 receptor antagonist (NK1RA) was nonsignificantly superior to a one-day dose of DEX with NK1RA as prophylaxis for delayed-onset nausea and vomiting. The absolute risk difference in complete response during the delayed phase was 9.0% among patients who received moderate emetogenic chemotherapy (MEC), and 12.3% among patients who received carboplatin. Therefore, we propose that the majority of patients, with the exception of patients who should receive minimal DEX, such as those intolerant to corticosteroids, should receive DEX beyond day one of treatment when receiving non-carboplatin MEC or carboplatin.

Introduction

Chemotherapy-induced nausea and vomiting (CINV) often reduces quality of life, treatment adherence, treatment efficacy, and curability in patients receiving chemotherapy. It is important to minimize the incidence of CINV to improve patients' quality of life and ensure they continue chemotherapy.

Although dexamethasone (DEX) is effective for suppressing CINV, short-term steroid use as antiemetic prophylaxis for chemotherapy can cause steroid-induced adverse

events such as elevated blood glucose levels,¹ reduced bone mineral density,² and other symptoms.³ Several studies and meta-analyses have shown that, as an antiemetic prophylaxis, the DEX-sparing strategy, which involves limiting administration of DEX to day one, in combination with palonosetron is non-inferior to multiple-day DEX.⁴⁻¹⁰ In terms of high emetogenic chemotherapy (HEC), a randomized phase III trial showed a one-day dose of DEX is non-inferior to a three-day dose of DEX in combination with neurokinin-1 receptor

antagonist (NK1RA) and palonosetron in patients receiving anthracycline plus cyclophosphamide therapy. On the other hand, a one-day dose of DEX was indicated to be insufficient to control CINV in patients receiving cisplatin-containing regimen.¹¹ Thus, global guidelines recommend continuous administration of DEX in the delayed phase (DP) for patients receiving cisplatin-containing chemotherapy.¹²⁻¹⁵

Recent guidelines classify carboplatin from a moderate emetogenic chemotherapy (MEC) to HEC,¹²⁻¹⁵ and recommend that patients receiving carboplatin area under the curve ≥ 4 mg/mL/min be offered triplet antiemetic prophylaxis, which combines a NK1RA with a 5-hydroxytryptamine-3 receptor antagonist (5HT3RA) and DEX.¹²⁻¹⁵ For patients receiving carboplatin, American Society of Clinical Oncology and Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) guidelines recommend combining a one-day DEX dose with NK1RA and 5HT3RA.^{14,15} However, the recently updated National Comprehensive Cancer Network (NCCN) guideline recommends the DEX-sparing strategy be limited to patients with few specific risk factors for CINV or intolerance to corticosteroids.¹² A recent trial by Iihara et al. showed that CINV associated with carboplatin occurs in the DP rather than the acute phase.¹⁶ A propensity score matching retrospective cohort study ($N = 56$) using data from a prospective observational study in clinical practice showed that a three-day dose of DEX was significantly superior to a one-day dose of DEX in triplet antiemetic prophylaxis for preventing nausea in patients receiving carboplatin.¹⁷

However, no randomized controlled trial (RCT) to date has examined the usefulness of combining DEX-sparing strategy with NK1RA in patients receiving carboplatin. For patients receiving non-carboplatin MEC, global guidelines recommend adding NK1RA to DEX and 5HT3RA as one antiemetic prophylaxis option,^{12,13} while the usefulness of combining the DEX-sparing strategy with NK1RA has not been established for these patients either. It is necessary to clarify the role of DEX in preventing delayed-onset CINV in triple antiemetic prophylaxis for patients receiving carboplatin and non-carboplatin MEC.

Therefore, we conducted a network meta-analysis (NMA) to compare one-day and three-day DEX in combination with NK1RA for preventing CINV associated with carboplatin and non-carboplatin MEC.

Patients and Methods

Objectives

The present study aimed to compare one-day versus three-day DEX in combination with NK1RA and 5HT3RA for preventing CINV associated with carboplatin and non-carboplatin MEC described in the most recent NCCN guideline.¹² The present NMA was prospectively registered (PROSPERO registration number: CRD42021256346) and was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Inclusion and Exclusion Criteria

Randomized (phase II or III) clinical trials were included if they were published in English. Trials of interest were those that compared the efficacy of globally available antiemetics in adult patients with cancer receiving carboplatin or non-carboplatin MEC. Trials that compared two of the following

antiemetic strategies were included: (1) three-day DEX with NK1RA (3-DEX + NK1RA), (2) one-day DEX with NK1RA (1-DEX + NK1RA), (3) three-day DEX (3-DEX), and (4) one-day DEX (1-DEX). Studies that used drugs other than DEX, 5HT3RA, and NK1RA for antiemetic prophylaxis, such as olanzapine or metoclopramide, were excluded.

Outcome Measures

The primary outcome was complete response (CR; no emesis and no rescue medication) during the DP (24-120 h after chemotherapy initiation). The secondary outcome was no nausea during the DP (NN-DP). For the primary outcome, subgroup analysis was performed in patients who received carboplatin-based chemotherapy and those who received a three-day dose of first-generation 5HT3RA or single dose of palonosetron (long 5HT3RA). All outcome variables were extracted in the first planned chemotherapy cycle.

Study Selection and Data Extraction

We systematically searched for eligible RCTs published through May 15, 2021 using PubMed and Ovid-MEDLINE. We used a combination of the terms “chemotherapy-induced nausea and vomiting,” “moderately emetogenic chemotherapy,” “steroid-sparing,” “neurokinin-1 receptor antagonists,” “fosaprepitant,” “ezlopitant,” “netupitant,” “rolapitant,” and “aprepitant” to find relevant articles (see [Supplementary Table S1](#) for details). An additional search through the reference lists of relevant reviews and meta-analyses was also conducted. Two reviewers (D.W. and H.I.) independently assessed the abstracts of all relevant studies to confirm their eligibility and extracted details from the included studies, including the study design, study population characteristics, inclusion criteria, outcome measures, chemotherapy regimen, and details of the antiemetic regimen. Decisions made by each of the two reviewers were compared, and any disagreement was resolved through consensus between the two reviewers.

Risk of Bias Assessment

Two reviewers (D.W. and H.I.) independently assessed the risk of bias due to the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported results, and other biases of the included studies ([Supplementary Table S2](#)) using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) by The Cochrane Collaboration (<http://www.cochrane.de>). Any disagreement was resolved through consensus between the two reviewers.

Statistical Analysis

An arm-based NMA using Bayesian methods was conducted to compare multiple antiemetic strategies. NMA enables the direct comparison of treatments in individual trials and indirect comparison between trials simultaneously.¹⁸ In particular, an arm-based approach can be used estimate the population-averaged treatment-specific event rate. The proportions of CR-DP and NN-DP in each antiemetic strategy were aggregated using the `nma.ab.bin` function in the R package, `pnetmeta`.¹⁹ The statistical heterogeneity in each treatment arm was evaluated using the `I2` statistic with the `metaprop` function in the R package, `meta`. An `I2 > 50%` indicated statistically significant heterogeneity ([Supplementary Table S3](#)). A random effects model was used to consider heterogeneity, and the correlations between treatments were

assumed to be different. Final estimation routines used 3 chains of 10 000 burn-in iterations, with 50 000 estimation iterations without thinning, resulting in 120 000 iterations for analysis. The results of NMA were estimated using posterior median with corresponding 95% credible intervals (CIs), which can be interpreted in the same manner as 95% confidence intervals. Statistical significance was indicated when the lower limit of one 95% CI exceeded the upper limit of the other 95% CI.

Results

Eligible Studies and Characteristics

Figure 1 shows a flow diagram of the study selection process. Among the 745 published papers on CINV identified by searching databases, we focused on 24 potentially relevant randomized control trials. We further excluded several trials because they did not use corticosteroids as an antiemetic prophylaxis ($n = 2$)^{20,21}; used casopitant, which is not approved by the U.S. Food and Drug Administration, as an antiemetic prophylaxis ($n = 1$)²²; used a crossover design and did not report the outcomes of the first chemotherapy ($n = 1$)²³; examined chemotherapy including multiple day administration of MEC ($n = 2$)^{24,25}; or did not examine the endpoints of interest for this study ($n = 1$).²⁶ Ultimately, 17 trials were included in our analyses.^{5,27-42} One article⁴³ was a post-hoc analysis of another eligible study³⁸; the former was used for subgroup analyses.

Table 1 summarizes the characteristics of all included trials. Eight trials compared 3-DEX + NK1RA and 3-DEX,^{27,30,31,33,34,36,39,40} five trials compared 1-DEX + NK1RA and 1-DEX,^{32,37,38,41,42} and four trials compared 3-DEX and 1-DEX,^{5,28,29,35} while no trials directly compared 3-DEX + NK1RA with 1-DEX + NK1RA (Supplementary Figure S1). Of the 4534 patients included this NMA, 11.0% ($n = 499$) received 3-DEX + NK1RA, 31.7% ($n = 1438$) received 1-DEX + NK1RA, 18.5% ($n = 839$) received 3-DEX, and 38.8%

($n = 1758$) received 1-DEX. The proportion of patients who received carboplatin-based chemotherapy was 49.6% ($n = 2250$). Among those administered NK1RAs, 57.5% ($n = 1113$) received aprepitant, 25.9% ($n = 502$) received fosaprepitant, and 16.6% ($n = 322$) received rolapitant. Among those administered 5HT3RAs, 42.4% ($n = 1923$) received a first-generation 5HT3RA on day one only, 35.4% ($n = 1603$) received a first-generation 5HT3RA from day one to three, and 19.7% ($n = 895$) received palonosetron. The type of 5HT3RA administered to the remaining 2.5% ($n = 113$) was unclear.

Proportion Experiencing CR-DP and NN-DP in Each Antiemetic Regimen

The proportion of patients who experienced CR-DP was 82.5% (95% CI, 73.9-88.6), 73.5% (95% CI, 62.8-80.9), 70.4% (95% CI: 63.3-76.3), and 65.5% (95% CI, 57.8-72.2) among those who received 3-DEX + NK1RA, 1-DEX + NK1RA, 3-DEX, and 1-DEX, respectively (Figure 2). Meanwhile, the proportion who experienced NN-DP was 67.9% (95% CI, 54.9-79.3), 42.8% (95% CI, 15.2-81.5), 51.6% (95% CI, 35.5-65.9%), and 35.4% (95% CI, 12.4-72.3) among patients who received 3-DEX + NK1RA, 1-DEX + NK1RA, 3-DEX, and 1-DEX, respectively (Figure 3).

Among patients who received carboplatin-based chemotherapy, the proportion who experienced CR-DP was 86.9% (95% CI, 75.5-93.3), 74.4% (95% CI, 57.8-85.2), 70.5% (95% CI, 59.3-79.3), and 61.6% (95% CI, 48.7-72.8) of those who received 3-DEX + NK1RA, 1-DEX + NK1RA, 3-DEX, and 1-DEX, respectively (Figure 4). Meanwhile, among patients who received long 5HT3RA, the proportion who experienced CR-DP was 86.9% (95% CI, 71.2-94.3), 75.1% (95% CI, 44.0-91.4), 71.0% (95% CI, 60.7-79.3), and 67.4% (95% CI, 59.9-74.0) of those who received 3-DEX + NK1RA, 1-DEX + NK1RA, 3-DEX, and 1-DEX, respectively (Figure 5).

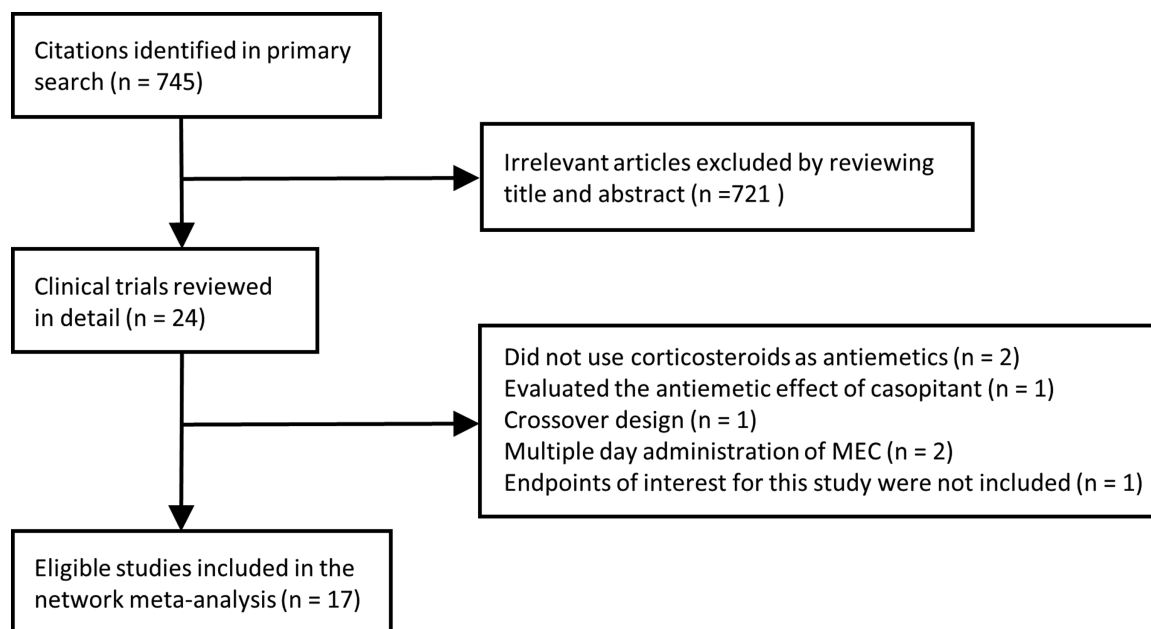


Figure 1. PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Study characteristics and patient demographics of studies included in the network meta-analysis

Study name	Major chemotherapy regimen	NK1RA	5HT3RA	DEX	N (male/female)	Carboplatin-based regimen (%)	CR-DP	NN-DP
Aridome_2016	Oxaliplatin-based	APR	Any 5HT3RA	3-day	59 (34/25)	0	47/59	38/59
		—	Any 5HT3RA	3-day	54 (30/24)	0	43/54	37/54
Celio_2011	Carboplatin-based	—	Palo	3-day	100	16 (16.0)	76/100	NA
	Oxaliplatin-based	—	Palo	1-day	111	21 (18.9)	79/111	NA
	Irinotecan-based	—	Palo	1-day	111	21 (18.9)	79/111	NA
Furukawa_2015	Carboplatin-based	—	Palo	3-day	39 (0/39)	39 (100)	30/39	25/39
		—	Palo	1-day	43 (0/43)	43 (100)	30/43	26/43
Ito_2014	Carboplatin-based	APR	First-generation 5HT3RA day 1	3-day	67 (56/11)	67 (100)	54/66	35/66
		—	First-generation 5HT3RA day 1	3-day	67 (54/13)	67 (100)	46/67	29/67
Kaushal_2015	Carboplatin-based	APR	Palo	3-day	30 (29/1)	30 (100)	25/30	23/30
		—	OND day 1-3	3-day	30 (23/7)	30 (100)	16/30	13/30
Kim_2017	Carboplatin-based	APR	OND day 1	1-day	237 (129/108)	156 (65.8)	176/237	NA
	Oxaliplatin-based	—	OND day 1-3	1-day	243 (134/109)	156 (64.2)	173/243	NA
	Irinotecan-based	—	OND day 1-3	1-day	243 (134/109)	156 (64.2)	173/243	NA
Komatsu_2015	Oxaliplatin-based	—	Palo	3-day	154 (87/67)	19 (12.3)	100/154	NA
	Irinotecan-based	—	Palo	1-day	151 (86/65)	18 (11.9)	101/151	NA
Kusagaya_2015	Carboplatin-based	APR	Palo	3-day	41 (29/12)	41 (100)	33/41	NA
		—	Palo	3-day	39 (28/11)	39 (100)	30/39	NA
Maehara_2015	Carboplatin-based	APR	GRA day 1	3-day	11 (0/11)	11 (100)	11/11	10/11
		—	GRN day 1	3-day	12 (0/12)	12 (100)	8/12	2/12
Matsuura_2015	Carboplatin-based	—	Palo	3-day	53 (0/53)	53 (100)	36/53	NA
		—	Palo	1-day	56 (0/56)	56 (100)	34/56	NA
Nishimura_2015	Oxaliplatin-based	APR	5HT3RA day 1	3-day	207 (126/81)	0	159/187	124/187
		—	5HT3RA day 1	3-day	206 (126/80)	0	138/183	113/183
Rapoport_2010	Carboplatin-based	APR	OND day 1	1-day	226	NA*	172/226	NA
	Irinotecan-based	—	OND day 1-3	1-day	203	NA*	140/203	NA
	Oxaliplatin-based	—	OND day 1-3	1-day	203	NA*	140/203	NA
	Other non-AC MEC	—	OND day 1-3	1-day	203	NA*	140/203	NA
Schwartzberg_2015	Carboplatin-based	ROL	GRN day 1-3	1-day	322	191 (59.3)	245/322	NA
	Irinotecan-based	—	GRN day 1-3	1-day	307	209 (68.1)	196/307	NA
	Oxaliplatin-based	—	GRN day 1-3	1-day	307	209 (68.1)	196/307	NA
	Other non-AC MEC	—	GRN day 1-3	1-day	307	209 (68.1)	196/307	NA
Sugimori_2017	Carboplatin-based	APR	Palo	3-day	39 (0/39)	39 (100)	38/39	27/39
		—	Palo	3-day	39 (0/39)	39 (100)	32/39	25/39
Tanioka_2013	Carboplatin-based	APR	GRN day 1	3-day	45 (0/45)	44 (97.8)	28/45	NA
		—	GRN day 1	3-day	46 (0/46)	45 (97.8)	24/46	NA
Weinstein_2016	Carboplatin-based	FAPR	OND day 1	1-day	502 (204/298)	257 (51.2)	396/502	NA
	Oxaliplatin-based	—	OND day 1-3	1-day	498 (205/293)	256 (51.4)	341/498	NA
Yahata_2016	Carboplatin-based	APR	First-generation 5HT3RA day 1	1-day	155 (0/155)	155 (100)	96/151	61/151
		—	First-generation 5HT3RA day 1	1-day	152 (0/152)	152 (100)	72/146	49/146

*Data could not be extracted from among the other chemotherapy regimens.

Abbreviations: 5HT3RA, serotonin receptor antagonist; APR, aprepitant; CR-DP, complete response during delayed phase; DEX, dexamethasone; FAPR, fos-aprepitant; GRN, granisetron; NA, not available; NK1RA, neurokinin-1 receptor antagonist; NN-DP, no nausea during delayed phase; OND, ondansetron; Palo, palonosetron; ROL, rolapitant.

Pairwise Comparison of 3-DEX + NK1RA and 1-DEX + NK1RA

Figure 6 shows the results of a pairwise comparison of 3-DEX + NK1RA and 1-DEX + NK1RA in CR-DP, NN-DP, and CR-DP in patients who received carboplatin-based chemotherapy

and in CR-DP in patients who received long 5HT3RA. While there were no significant differences in any outcome between 3-DEX + NK1RA and 1-DEX + NK1RA, 3-DEX + NK1RA tended to be superior to 1-DEX + NK1RA. The absolute risk difference between 3-DEX + NK1RA and 1-DEX + NK1RA

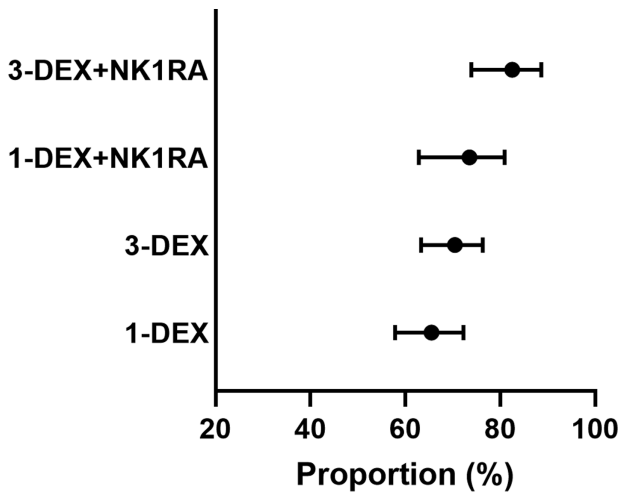


Figure 2. Proportion of patients who experienced complete response during the delayed phase in each antiemetic regimen among the entire population.

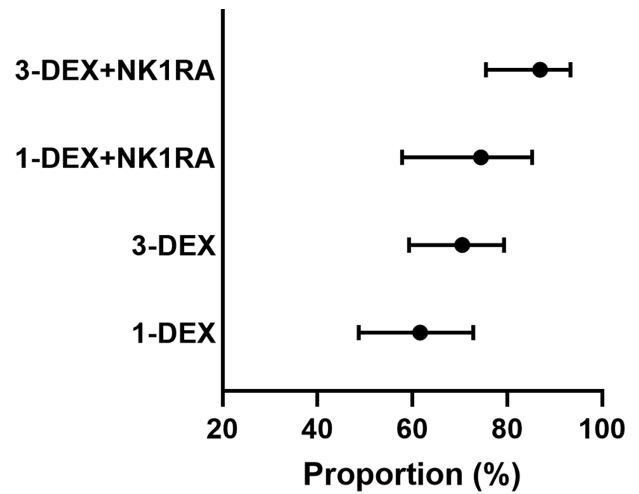


Figure 4. Proportion of patients who achieved complete response during the delayed phase in each antiemetic regimen among those who received a carboplatin-based regimen.

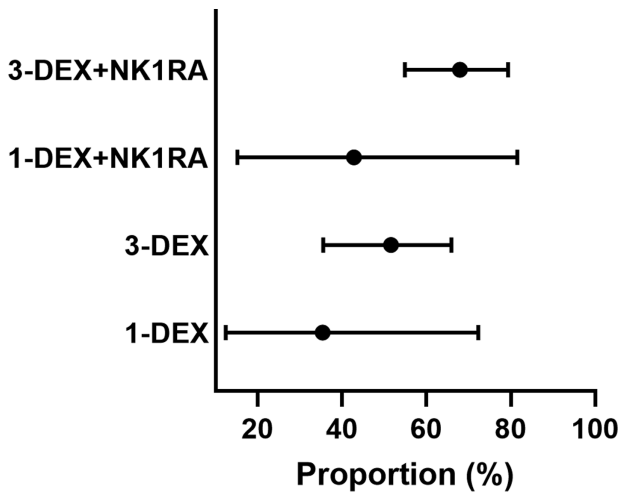


Figure 3. Proportion of patients who experienced no nausea during the delayed phase in each antiemetic regimen among the entire population.

was 9.0% (95% CI, -2.3 to 21.1), 24.7% (95% CI, -14.9 to 54.6), 12.3% (95% CI, -3.2 to 30.7), and 11.4% (95% CI, -10.1 to 42.4) in CR-DP, NN-DP, and CR-DP in patients who received carboplatin-based chemotherapy and in CR-DP in patients who received long 5HT3RA, respectively.

Discussion

We performed a systematic review and NMA to indirectly compare the antiemetic effects of 3-DEX + NK1RA and 1-DEX + NK1RA in patients receiving carboplatin and non-carboplatin MEC. Although we found no statistically significant differences, 3-DEX + NK1RA showed a tendency toward being superior to 1-DEX + NK1RA, and the absolute risk difference between 3-DEX + NK1RA and 1-DEX + NK1RA was 9.0% and 24.7% in CR-DP and NN-DP, respectively. These results suggest that continuous administration of DEX beyond day one may increase the benefits of prophylaxis for delayed-onset CINV in patients receiving carboplatin and non-carboplatin MEC.

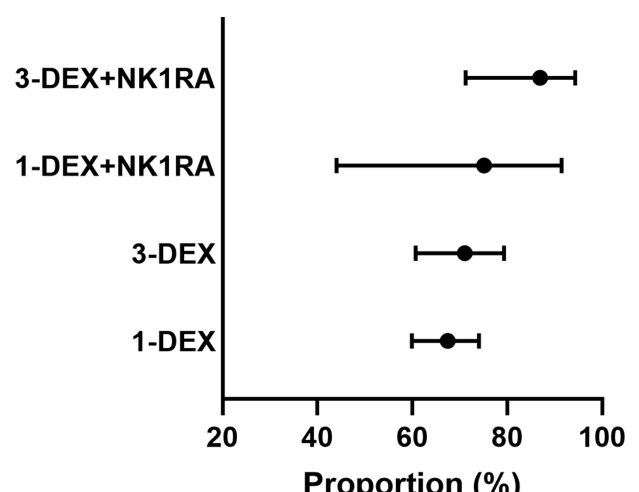


Figure 5. Proportion of patients who achieved complete response during the delayed phase in each antiemetic regimen among those treated with a three-day dose of first-generation 5HT3RA or single dose of palonosetron. 5HT3RA, 5-hydroxytryptamine-3 receptor antagonist.

Among patients who received carboplatin, we found that 3-DEX + NK1RA was nonsignificantly superior to 1-DEX + NK1RA in CR-DP, and that the absolute risk difference was 12.3%, which is clinically meaningful to the patient according to MASCC/ESMO.⁴⁴ Tamura et al. reported that the CINV incidence and severity associated with cisplatin and MEC comprising mainly carboplatin and oxaliplatin peaked on days four to five.⁴⁵ Iihara et al. reported that administration of carboplatin led to a high incidence of CINV that continued for more than seven days, with the severity peaking on days four to five with or without aprepitant.¹⁶ A propensity score matching retrospective cohort study that compared one-day versus three-day DEX with aprepitant and 5HT3RA for the prevention of CINV associated with carboplatin found that three-day DEX was significantly superior to one-day DEX for preventing nausea (82.5% vs. 44.4%). The study additionally found that the average severity of nausea was beyond “moderate” from day two in the one-day DEX group

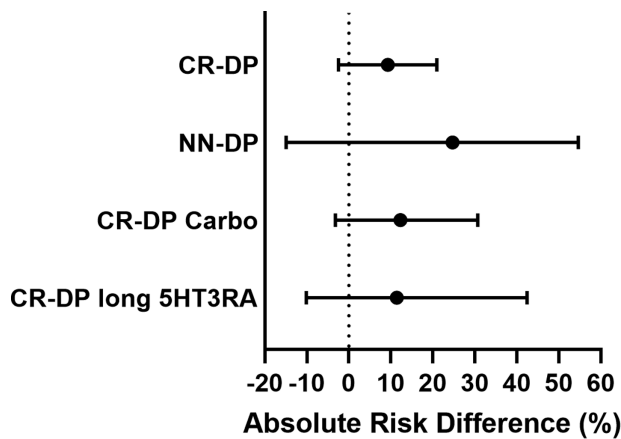


Figure 6. Pairwise comparison of 3-DEX + NK1RA and 1-DEX + NK1RA. Absolute risk difference greater than 1 suggests that 3-DEX + NK1RA is more efficient than 1-DEX + NK1RA. 1-DEX + NK1RA, one-day dexamethasone with neurokinin-1 receptor antagonist; 3-DEX + NK1RA, three-day dexamethasone with neurokinin-1 receptor antagonist.

compared to day five in the three-day DEX group.¹⁷ Thus, CINV associated with carboplatin during the delayed phase may be more difficult to control than that in the acute phase, and continuous DEX dosing beyond day one may play an important role in preventing delayed nausea. These results support our findings, which suggest that three-day DEX with NK1RA and 5HT3RA may be preferable for patients receiving triplet platinum-based chemotherapy, even if they are receiving triplet antiemetic prophylaxis.

We were unable to perform subgroup analysis of patients who received non-carboplatin MEC among the 3-DEX + NK1RA and 1-DEX + NK1RA groups due to insufficient data; thus, the superiority of 3-DEX + NK1RA over 1-DEX + NK1RA in non-carboplatin MEC remains unclear. However, given the benefit of 3-DEX + NK1RA over 1-DEX + NK1RA among the total population, continuous administration of DEX beyond day one may increase the benefit of prophylaxis for delayed-onset CINV in patients receiving non-carboplatin MEC. In particular, because oxaliplatin is known to induce a high incidence of delayed-onset nausea,^{45,46} DEX-sparing regimens should be used with caution in patients receiving oxaliplatin-based chemotherapy.

Delayed-onset nausea is an important part of CINV, and difficult to control.⁴⁷⁻⁴⁹ In this NMA, absolute risk difference between 3-DEX + NK1RA and 1-DEX + NK1RA in DP-NN was $\geq 20\%$. This result suggests extended DEX dose may play an important role to control delayed-onset nausea in triplet antiemetic prophylaxis with NK1RA. In previous phase III study, NK1RA did not significantly reduce visual analog scale for nausea compared to placebo.⁵⁰ Thus the addition of olanzapine should be considered when limiting administration of DEX to day one in patients with identifiable risk factors for CINV because olanzapine is possibly more effective than NK1RA for preventing nausea.⁵¹⁻⁵³

In this NMA, we classified patients who received a three-day dose of a first-generation 5HT3RA or single dose of palonosetron into the long 5HT3RA subgroup to examine them separately from patients who received single-day administration of 5HT3RA, and to set similar conditions for the effect of 5HT3RA on CINV in the delayed phase. In the long 5HT3RA group, 3-DEX + NK1RA showed a

nonsignificant superior effect to 1-DEX + NK1RA, and the absolute risk difference between 3-DEX and 1-DEX in CR-DP was 11.4%. The results of a prior RCT suggested that a one-day dose of DEX in combination with palonosetron and NK1RA was an insufficient antiemetic prophylaxis for a cisplatin-containing regimen.¹¹ In contrast, a recent study reported that the DEX-sparing strategy in combination with netupitant and palonosetron showed comparable antiemetic effects to four-day DEX in patients receiving cisplatin-based chemotherapy.⁵⁴ Future studies should examine the usefulness of the DEX-sparing strategy in combination with netupitant and palonosetron for carboplatin and non-carboplatin MEC.

Cost is an important factor when selecting antiemetic measures. DEX is less expensive than other antiemetic agents such as palonosetron and NK1RAs. Given that our results suggest there may be considerable benefits to continuous DEX administration, we propose that the majority of patients, with the exception of patients who should receive minimal DEX, such as those intolerant to corticosteroids, should receive DEX beyond day one of treatment.

This NMA has several limitations. First, many of our arguments are based on indirect comparisons between 3-DEX + NK1RA and 1-DEX + NK1RA, which cannot replace the direct comparisons obtained from randomized studies. Second, we could not examine the outcome for those using non-carboplatin MEC due to insufficient data. Further randomized studies are needed to determine the benefits of the DEX-sparing regimen in triplet antiemetic prophylaxis, especially those containing carboplatin and oxaliplatin, which have been shown to benefit from the addition of NK1RA and to lead to a high incidence of delayed-onset CINV.^{16,45,46,55} Third, individual studies in this population are relatively small, which significantly limits statistical power and sensitivity to detect differences. Despite these limitations, our findings, which were derived from available RCT data, highlight concerns related to using the DEX-sparing strategy in combination with NK1RA for the prevention of CINV in patients receiving carboplatin and non-carboplatin MEC.

Conclusion

Our NMA showed that a three-day dose of DEX with NK1RA tended to have greater antiemetic benefit than a one-day dose of DEX with NK1RA; the absolute risk difference between a three-day and one-day dose of DEX with NK1RA was 9.0% and 24.7% in CR-DP and NN-DP, respectively. Among patients who received carboplatin-based chemotherapy, the absolute risk difference in CR-DP between a three-day and one-day dose of DEX with NK1RA was 12.3%. Therefore, care is needed when choosing the DEX-sparing strategy with NK1RA for patients receiving carboplatin and non-carboplatin MEC. The strategy may be more suitable for selected patients, such as those with few identifiable risk factors for CINV.

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Conflict of Interest

Akitaka Makiyama: Eli Lilly Japan K.K., Taiho Pharmaceutical Co. Ltd, Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb Co. Ltd., and Daiichi Sankyo Co. Ltd (H). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board.

Author Contributions

Conception/design: D.W., H.I., H.F. Provision of study material/patients: D.W., H.I., S.N. Collection and/or assembly of data: D.W., H.I., S.N. Data analysis and interpretation: D.W., H.I., A.S. Manuscript writing: D.W., H.I., A.S., A.M. Final approval of manuscript: All authors.

Data Availability

The data underlying this article are available in the article and in its online supplementary material.

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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