

Efficacy and safety of dexamethasone sparing for the prevention of nausea and vomiting associated with highly emetogenic risk antineoplastic agents: a systematic review and meta-analysis of the Clinical Practice Guidelines for Antiemesis 2023 from the Japan Society of Clinical Oncology

Authors: Ayako Yokomizo¹, Kazuhisa Nakashima², Arisa Iba³, Kenji Okita⁴, Makoto Wada⁵, Keiko Iino⁶, Tatsuo Akechi⁷, Hirotooshi Iihara⁸, Chiyo K. Imamura⁹, Ayako Okuyama¹⁰, Keiko Ozawa¹¹, Yong-Il Kim¹², Hidenori Sasaki¹³, Eriko Satomi¹⁴, Masayuki Takeda¹⁵, Ryuhei Tanaka¹⁶, Takako Eguchi Nakajima¹, Naoki Nakamura¹⁷, Junichi Nishimura¹⁸, Mayumi Noda¹⁹, Kazumi Hayashi²⁰, Takahiro Higashi²¹, Narikazu Boku²², Koji Matsumoto²³, Yoko Matsumoto²⁴, Nobuyuki Yamamoto²⁵, Kenjiro Aogi²⁶, Masakazu Abe²⁷

¹ Department of Early Clinical Development, Kyoto University Graduate School of Medicine: 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto, 606-8507, Japan

² Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane, Japan

³ Institute for Global Health Policy Research, Bureau of International Health Cooperation, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku, Tokyo, 162-8655, Japan

⁴ Department of Surgery, Otaru Ekisaikai Hospital, 1-4-1, Inaho, Otaru, Hokkaido, Japan

⁵ Department of Psycho-Oncology and Palliative Medicine, Osaka International Cancer Institute, Otemae 3-1-69, Chuo-ku, Osaka 541-8567, Japan

⁶ School of Nursing, National college of Nursing School of Nursing, National college of Nursing, Japan, 1-2-1, Umezono, Kiyose, Tokyo, 204-8575, Japan

⁷ Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, 1 Kawasumi, Mizuho-cho, Mizuho-ku, Nagoya 467-8601, Japan

⁸ Department of Pharmacy, Gifu University Hospital, 1-1 Yanagido, Gifu, Gifu, 501-1194, Japan

⁹ Advanced Cancer Translational Research Institute, Showa University, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142-8555, Japan

¹⁰ Graduate School of Nursing Science, St. Luke's International University, 10-1 Akashi-cho, Chuo-ku, Tokyo, 104-0044, Japan

¹¹ Division of Survivorship, Institute for Cancer Control, National Cancer Center, 5-1-1 Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

¹² Division of Medical Oncology, Yodogawa Christian Hospital, 1-7-50 Kunijima, Higasiyodogawa-ku, Osaka Prefecture

¹³ Division of Medical Oncology, Hematology and Infectious Disease, Fukuoka University Hospital, 7-45-1, Nanakuma, Jonan-Ku, Fukuoka, Fukuoka, 814-0180, Japan.

¹⁴ Department of Palliative Medicine, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

¹⁵ Department of Cancer Genomics and Medical Oncology, Nara Medical University, 840 Shijo-Cho, Kashihara, Nara, 634-8521, Japan

¹⁶ Department of Pediatric Hematology/Oncology, International Medical Center, Saitama Medical University, 1398-1 Yamane, Hidaka, Saitama 350-1298, Japan

¹⁷ Department of Radiation Oncology, St. Marianna University, 2-16-1, Sugao, Miyamae, Kawasaki, Kanagawa, 216-8511, Japan

¹⁸ Department of Gastroenterological Surgery, Oisana International Cancer Institute, 3-1-69, Otemae, Chuoku, Osaka, 541-8567, Japan

¹⁹ Non-profit Organization Sasaeau-kai "Alpha", 518-7 Kawado-cho, Chuo-ku, Chiba-shi, Chiba, 260-0802, Japan

²⁰ Department of Clinical Oncology and Hematology, The Jikei University school of Medicine. 3-25-8 Nishi-shinbashi Minatoku, Tokyo, Japan

²¹ Department of Public Health and Health Policy, The University of Tokyo. 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-0033, Japan

²² Department of Oncology and General Medicine, IMSUT Hospital, Institute of Medical Science, University of Tokyo, 4-6-1, Shiroganedai, Minatoku, Tokyo, 108-8639, Japan

²³ Division of Medical Oncology, Hyogo Cancer Center, 13-70 Kitaoji-cho, Akashi, Hyogo, 673-0021, Japan

²⁴ Non-profit Organization Ehime Cancer Support "Orange-no-kai", 3-8-24 FurukawaMinami, Matsuyama, Ehime, Japan

²⁵ Internal Medicine III, Wakayama Medical University, Kimiidera 811-1, Wakayama, Wakayama 541-8509

²⁶ Department of Breast Surgery, National Hospital Orgnaization Shikoku Cancer Center, 160 Kou, Minamiumemoto-matchi, Matsuyama, Ehime, 791-0280, Japan

²⁷ Department of Obstetrics and Gynecology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Chuo-Ku, Hamamatsu, Shizuoka 431-3192, Japan

Corresponding author

Kazuhisa Nakashima

Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Shimane University Faculty of Medicine, 89-1 Enya-cho, Izumo, Shimane, 693-8501, Japan

Tel: (+81) 853-20-2580

Fax: (+81) 853-20-2581

E-mail: kazuhin@med.shimane-u.ac.jp

1 **Abstract**

2 **Background:** Chemotherapy-induced nausea and vomiting (CINV) are
3 common side effects, classified according to timing and severity.
4 Conventional agents such as dexamethasone are effective but have various
5 side effects. For moderately emetogenic chemotherapy, dexamethasone-
6 sparing antiemetic therapies have been developed to minimize these side
7 effects. This systematic review evaluated the efficacy and safety of
8 dexamethasone-sparing antiemetic therapy for highly emetogenic
9 chemotherapy (HEC).

10 **Methods:** We performed a thorough literature search for studies related to

11 dexamethasone-sparing antiemetic therapy with neurokinin-1 antagonists

12 (NK₁RA) for HEC using the PubMed, Cochrane Library, and Ichushi-Web

13 databases. A qualitative analysis of the combined data was performed, and

14 risk differences with confidence intervals were calculated.

15 **Results:** Two reviewers independently assessed the 425 records, and 12 full-

16 text articles were evaluated for eligibility. Two studies were included in the

17 qualitative and meta-analyses. These studies included anthracycline-

18 cyclophosphamide (AC) regimens and cisplatin-based regimens, with

19 palonosetron as the serotonin receptor antagonist. In the two studies, no
20 difference was found in the prevention of vomiting (delayed complete
21 response). However, non-inferiority was not demonstrated in the subgroup
22 that received cisplatin-containing regimens. Delayed complete control
23 showed different results for nausea prevention; however, there was no
24 significant difference in the meta-analysis. Only one report has shown non-
25 inferiority for delayed total control. Although the strength of evidence for
26 individual outcomes varied, there was no difference in the duration of
27 dexamethasone administration.

28 **Conclusions:** This systematic review and meta-analysis revealed that

29 dexamethasone-sparing antiemetic therapy with NK₁RA and palonosetron

30 can be used to prevent CINV in HEC, limited to AC combination therapy.

31

32 Keywords: dexamethasone; highly emetogenic chemotherapy;

33 chemotherapy-induced nausea and vomiting; sparing; meta-analysis

34

35 **Introduction**

36 Chemotherapy-induced nausea and vomiting (CINV) are common

37 distressing adverse reactions to chemotherapy. It is typically classified as

38 acute (within the first 24 h after chemotherapy initiation), delayed (24–120 h

39 after chemotherapy initiation), anticipatory, breakthrough, or refractory.

40 Intravenous chemotherapy regimens are categorized according to the

41 incidence of emesis as follows: high emetic risk, 90% or more patients

42 experience acute emesis; moderate emetic risk, 30–90% of patients

43 experience acute emesis; low emetic risk, 10–30% of patients experience

44 acute emesis; and minimal emetic risk, fewer than 10% of patients

45 experience acute emesis [1]. Dexamethasone (DEX), a traditional antiemetic

46 drug, is commonly recommended in various supportive care guidelines for

47 the prevention of acute and delayed CINV caused by emetogenic

48 chemotherapy [1-4]. In contrast, new antiemetic drugs, such as second-

49 generation serotonin receptor antagonists (5HT₃RA) and neurokinin-1

50 receptor antagonists (NK₁RA) have been developed. Although DEX is

51 generally considered safe for the prevention of nausea and vomiting,

52 corticosteroids can cause a range of side effects such as insomnia, reduced

53 bone mineral density, and hyperglycemia [5-7]. Therefore, antiemetic
54 therapy has been established for moderately emetogenic chemotherapy
55 (MEC), especially the anthracycline-cyclophosphamide combination (AC)
56 regimen, with the addition of new antiemetic agents and sparing of DEX [8].
57 International guidelines recommend DEX-sparing regimens as an option for
58 antiemetic therapy of MEC [2,4,9]. However, previous reports on DEX
59 sparing in AC therapy for MEC indicate that NK₁RA was not used in
60 combination. The AC regimen has recently been considered highly
61 emetogenic chemotherapy (HEC), for which the addition of NK₁RA to

62 CINV control is recommended [2-4]. Additionally, DEX sparing in other
63 HEC regimens (i.e. cisplatin-containing regimens) has also been studied;
64 thus, we performed a systematic literature review to evaluate the efficacy
65 and safety of DEX-sparing antiemetic therapy with NK₁RA for HEC
66 regimens, which will assist in updating clinical guidelines for antiemetic
67 therapies [1].

68

69 **Methods**

70 A qualitative and quantitative systematic review was conducted based on the

71 Minds Handbook for Clinical Practice Guideline Development 2017 [10]. For

72 DEX-sparing therapy for CINV using HEC, the importance of outcomes was

73 reviewed based on the Minds Handbook [10]. An increased incidence of

74 CINV due to DEX sparing was considered a harmful outcome, whereas the

75 suppression of elevated blood glucose and osteoporosis were considered

76 beneficial outcomes.

77

78 **Search strategy**

79 The PubMed, Cochrane Library, and Ichushi-Web databases were searched

80 using the terms, “highly emetogenic chemotherapy,” “chemotherapy-induced

81 nausea and vomiting,” “nausea,” “vomiting,” “dexamethasone,”

82 “corticosteroid,” “sparing,” “side effect,” “cisplatin,” “AC,” “CINV,” and

83 “HEC.” The search covered the period from January 1, 1990, to December 31,

84 2020.

85 Initial screening was independently performed by two authors (AY and KN)

86 based on the titles and abstracts of all extracted articles, followed by full-text

87 screening (i.e., second screening) according to the inclusion and exclusion

88 criteria. The authors were allowed to independently search the articles and

89 add them to the list if they met all the inclusion criteria (manual search). The

90 reasons for exclusion were recorded and duplicates were removed. Any

91 disagreements were resolved by a third author. The articles were examined

92 for data quality according to the selection criteria outlined in the following

93 sections.

94

95 **Selection criteria**

96 Inclusion criteria were as follows: (1) studies with randomized controlled trial
97 (RCT), non-RCT, and a cohort or case-control trial designs; (2) studies with
98 an adult population who received HEC; (3) studies that compared NK₁RA
99 plus single-dose DEX (with or without an active agent) to the same antiemetic
100 regimen on day 1 followed by either no further DEX or additional DEX doses
101 (both alone or in combination with another active agent) on the subsequent
102 days for the prevention of CINV following single-day HEC regimens.
103 Systematic reviews were eligible when they were judged to be of moderate
104 quality according to AMSTAR [11] and included studies fulfilled the

105 inclusion criteria. We also excluded guidelines, reviews, letters, abstracts
106 without articles, laboratory studies, case reports, and studies published in
107 languages other than Japanese or English.

108

109 **Data extraction and quality assessment**

110 After the second screening, the author (A.Y.) of the systematic review team
111 reassessed the articles and extracted data using standardized data abstraction
112 forms. The evidence indicated by individual studies related to critical
113 outcomes included within the clinical questions posed by the guideline-

114 creation team was divided into groups based on study design and quality. The

115 following four outcome indicators were evaluated: (1) prevention of vomiting,

116 (2) prevention of nausea, (3) prevention of elevated blood glucose levels, and

117 (4) prevention of osteoporosis. The authors determined the outcomes of the

118 Population, Intervention, Comparator, and Outcome (PICO) framework on

119 both the benefits and harms of sparing the administration of DEX for one day

120 for the prevention of nausea and vomiting associated with HEC. The leader

121 (M.A.) of the guideline-creation team resolved conflicts and questions. The

122 level of evidence was evaluated for each study outcome grouped by study

123 design. The certainty of the evidence was assessed based on the risk of bias,
124 inconsistency, imprecision, indirectness, and publication bias. The literature
125 quality and body of evidence were evaluated using the Grading of
126 Recommendations, Assessment, Development, and Evaluation (GRADE)
127 approach and then classified into four levels: “strong,” “medium,” “weak,”
128 and “very weak” [12].

129

130 **Statistical methodology**

131 Review Manager (Cochrane Collaboration, London, UK) version 5.3. was
132 used for the statistical analyses. After quantitative analysis using Excel,
133 studies were considered eligible and included in the meta-analysis if they
134 were designed to compare DEX on day 1 with sparing on subsequent days,
135 combined with NK₁RA, to the several-day use of DEX in HEC. The risk
136 difference (RD) for each endpoint was calculated and the effect size was
137 described as the 95% confidence interval (CI) for each study, using random-
138 effects models, depending on the level of heterogeneity. A forest plot was used
139 to graphically present the results of the calculated RD for the individual

140 studies and overall meta-analysis. The degree of heterogeneity was assessed

141 using I^2 and chi-squared-based Q-tests. Statistical significance was set at p

142 <0.05. A funnel plot was used to graphically investigate potential publication

143 bias.

144

145 **Results**

146 **Literature search**

147 The initial search yielded 421 results: PubMed, 72; Cochrane Library, 252;

148 and Ichusi-Web, 97 (date of search: February 25, 2021). An additional four

149 articles were manually searched and selected for inclusion. Among the 425
150 articles obtained, 423 were excluded after screening for noncompliance with
151 the previously outlined selection criteria, resulting in two articles being
152 included (Fig. 1) [13,14]. The primary reason for exclusion was the absence
153 of NK₁RA administration.

154 **Studies selected for the meta-analysis**

155 Two RCTs were included in the descriptive qualitative analysis and examined
156 in the meta-analysis. Table 1 summarizes the characteristics of the included
157 studies. They were selected for the meta-analysis of delayed complete

158 response (CR), delayed complete control (CC), and delayed total control (TC)

159 rates. We defined the delayed CR rate as an indicator of the prevention of

160 vomiting, and the delayed CC and TC rates as indicators of the prevention of

161 nausea.

162 **Association between each outcome using the PICO framework and DEX**

163 **sparing for the prevention of CINV caused by HEC**

164 **Association between the prevention of chemotherapy-induced vomiting**

165 **and DEX sparing**

166 This outcome was defined as delayed CR rate. The two evaluable RCTs

167 included 476 chemotherapy-naïve patients who received HEC. They were

168 over 20 years old and Japanese. One RCT was a phase II, single-center, single-

169 blind, placebo-controlled, parallel, randomized trial that included only female

170 patients with histologically confirmed breast cancer who received an

171 anthracycline-cyclophosphamide combination regimen. Another RCT was a

172 phase III, multicenter, double-blind, placebo-controlled randomized trial that

173 included patients with cancer who received HEC. In both trials, the antiemetic

174 regimen contained palonosetron as a 5HT₃RA and a NK₁RA (aprepitant or

175 fosaprepitant). The results of the meta-analysis revealed no significant

176 difference in the delayed CR rate between administering DEX only on the

177 first day and administration of DEX for three days in HEC, and there was no

178 publication bias (RD 0.0 [95% CI: -0.11–0.12], $p=0.95$) (Fig. 2). However, in

179 the latter RCT, non-inferiority was not demonstrated among the patients who

180 received cisplatin (CDDP)-containing regimens. Moreover, the duration of

181 DEX treatment in this study was shorter than that of the standard therapy.

182 Therefore, the results of this meta-analysis are applicable only to AC

183 regimens. The quality/certainty of evidence on this outcome was rated as

184 "medium."

185 **Association between the prevention of chemotherapy-induced nausea**

186 **and DEX sparing**

187 This outcome was defined as the delayed CC and TC rates. A delayed CC rate

188 was reported in two RCTs, whereas the TC rate was reported in only one RCT.

189 Therefore, a meta-analysis was conducted to determine the rate of delayed

190 CC. Regarding the delayed CC rate, one phase III RCT did not demonstrate

191 non-inferiority among all patients and in both subgroups (AC- or CDDP-

192 containing regimens), but one phase II RCT showed no significant difference.

193 However, the results of the meta-analysis showed low heterogeneity and no

194 publication bias, and there was no difference between the groups: DEX

195 administered on day 1 only and the 3-day use of DEX (RD -0.03 [95% CI: -

196 0.13–0.06], $p=0.53$) (Fig. 3). The quality/certainty of evidence on this

197 outcome was rated as "medium."

198 In contrast, one valuable RCT on the delayed TC rate demonstrated the non-

199 inferiority of DEX administered on day 1 compared with the 3-day use of

200 DEX (RD -0.03 [95% CI: -0.13–0.06], p=0.007). The quality/certainty of

201 evidence on this outcome was rated as "weak."

202 **Association between the prevention of blood glucose level elevation and**

203 **DEX sparing**

204 Although this outcome was initially established, no study has evaluated this

205 relationship. Therefore, we concluded that this could not be confirmed.

206 **Association between the prevention of osteoporosis and DEX sparing**

207 Although an association between the prevention of osteoporosis and DEX

208 sparing was initially established, no study has evaluated this relationship.

209 Therefore, we concluded that this could not be confirmed.

210

211 **Discussion**

212 This systematic review and meta-analysis demonstrate that DEX-sparing

213 antiemetic therapy with NK₁RA is applicable for preventing CINV in HEC

214 regimens, only for AC regimens. Since the classification of AC therapy as

215 HEC, there have only been two studies on DEX-sparing in combination with

216 NK₁RA in HEC. We conducted a meta-analysis to determine the appropriate
217 recommendations for the guidelines. To the best of our knowledge, this is the
218 only systematic review and meta-analysis to evaluate the efficacy and safety
219 of DEX sparing in combination with NK₁RA and palonosetron for the
220 prevention of CINV in HEC, including AC therapy.

221 Prevention of chemotherapy-induced vomiting was evaluated based on the
222 delayed CR rate. There was no significant difference between DEX
223 administration for 1 and 3 days. In contrast, the prevention of chemotherapy-
224 induced nausea was evaluated based on delayed CC and TC rates. The results

225 of the two RCTs were slightly different regarding delayed CC rate. However,

226 the results of the meta-analysis revealed no significant differences. This

227 discrepancy may be due to differences in patient numbers, patient

228 characteristics, and statistical methods (superiority or non-inferiority)

229 between the two studies. Only one RCT reported delayed TC rates,

230 demonstrating the non-inferiority of DEX sparing.

231 This review did not evaluate the outcomes of benefits, such as the incidence

232 of elevated blood glucose levels and osteoporosis outcomes, because no RCTs

233 addressed them. It has been reported that 20% of patients develop diabetes

234 when dexamethasone is used as an antiemetic for more than three cycles of

235 HEC or MEC [7]. Additionally, patients with gastrointestinal cancer who

236 regularly received DEX as antiemetic therapy reported decreased bone

237 density and increased bone formation markers after 16 weeks of

238 chemotherapy [6]. These studies suggest potential long-term risks associated

239 with DEX use, but it remains uncertain whether DEX sparing mitigates these

240 risks. In addition, Ito et al. reported that, although shortening the duration of

241 DEX administration may reduce hot flashes and tremors, the possibility that

242 anorexia and fatigue are suppressed by DEX cannot be ruled out [13].

243 Therefore, when considering DEX sparing, it is important to recognize that

244 there may be differences in outcomes beyond the control of nausea and

245 vomiting. It is necessary to thoroughly consider the balance of benefits and

246 risks as well as the patient's lifestyle, values, and preferences.

247 Although outside the scope of the current research, other studies have

248 demonstrated the efficacy of DEX-sparing in different antiemetic therapies

249 for CDDP-based chemotherapy. Minatogawa et al. [15] demonstrated the

250 non-inferiority of DEX sparing on days 2–4 for CR rates during the delayed

251 phase when combined with palonosetron, NK₁RA, and 5 mg olanzapine. This

252 report examined DEX sparing in standard antiemetic therapy for HEC, which

253 is a four-drug combination therapy. Moreover, Celio et al. showed that DEX

254 sparing with netupitant/palonosetron (NEPA) was not inferior to standard

255 therapy in overall and delayed CR rates [16]. However, it is important to

256 interpret this study by noting that NEPA has not yet been approved in Japan.

257 Additionally, statistical settings, such as sample size, should be taken into

258 consideration. While these studies suggest that DEX-sparing is feasible in

259 patients receiving CDDP, it is also necessary to note that the overall and

260 delayed no nausea rates were lower in the DEX-sparing group. Further studies

261 are needed to clarify whether DEX sparing in CINV prevention with CDDP
262 is feasible. Delayed CR, CC, and TC rates were used to assess the prevention
263 of CINV; CC, and TC differed in regarding nausea. In fact, in one phase III
264 RCT, the CC and TC rates were inconsistent. CC includes mild nausea,
265 therefore, administering DEX on days 2–3 might reduce nausea in the delayed
266 phase. Additionally, the subgroup analysis in the same RCT did not show non-
267 inferiority of delayed CR rate in regimens including CDDP and delayed CC
268 rate overall and in both subgroups. However, a combined analysis of two
269 RCTs on DEX sparing in CDDP-treated patients found no difference in

270 delayed CR and CC rates between the DEX-sparing and control groups [17].

271 A meta-analysis of AC regimens also showed no difference in delayed CC

272 and TC rates with DEX sparing [8]. These results suggested that there may be

273 no negative effects on the prevention of CINV in HEC-treated patients.

274 Notably, delayed CC rates are lower than delayed CR rates in two studies of

275 our review, and nausea control is inadequate even in the group receiving DEX

276 as usual. Netupitant/fosnetupitant may be more effective than

277 aprepitant/fosaprepitant in controlling delayed nausea [18,19]. The addition

278 of olanzapin has also been reported to substantially improve delayed nausea

279 control [20]. Saving DEX with these agents is expected to improve CC and

280 TC rates.

281 This study had several limitations. First, in the two RCTs included in this

282 study, the standard comparator treatment differed from the guideline-

283 recommended antiemetic therapy. Olanzapine was not administered

284 adjunctively, dexamethasone was administered for 3 days, and palonosetron

285 was administered at 0.75 mg (Japan only), making the control group different

286 from the standard treatment. Additionally, this study included only Japanese

287 patients. Therefore, although there were no differences in the results of this

288 meta-analysis, careful patient and antiemetic selection is deemed necessary

289 when considering DEX sparing in patients receiving HEC. Second, the

290 outcomes regarding the benefits of DEX sparing, such as suppression of

291 elevated blood glucose levels and osteoporosis outcomes, could not be

292 evaluated. Evidence regarding the effects of long-term intermittent steroid use

293 as an antiemetic therapy is limited, and further investigation is warranted.

294 The results of the systematic review did not evaluate the benefit of shortening

295 the duration of DEX treatment, but the negative effects did not differ from

296 that of standard therapy, suggesting that DEX-sparing may be useful in

297 patients receiving AC therapy. In the future, development and evaluation of

298 steroid-sparing antiemetic therapies that adequately control nausea for HEC

299 containing CDDP are necessary to improve quality of life and treatment

300 acceptability for patients with cancer.

301

302 **Acknowledgements**

303 The authors are grateful to Mr. Naohiko Yamaguchi and Ms. Yuko Mitsuoka

304 for their contributions in the initial literature search. The authors thank Ms.

305 Kyoko Hamada and Ms. Natsuki Fukuda for their valuable comments and

306 recommendations. We would like to thank Editage (www.editage.jp) for the

307 English language editing.

308

309 **Author contributions**

310 All authors contributed to the conception and design of this study. A.Y. wrote
311 the draft of the manuscript and all authors reviewed and commented on the
312 manuscript. All the authors have read and approved the final manuscript.

313

314 **Funding**

315 This study was supported by Japan Society of Clinical Oncology.

316

317 **Data availability**

318 The data associated with this systematic review can be accessed from the

319 corresponding author upon reasonable request.

320

321 **Ethical approval**

322 Not applicable

323

324 **Informed consent**

325 Formal consent was not required for this type of study. Not applicable.

326

327 **Conflicts of interest**

328 Kazuhisa Nakashima received honoraria from Taiho Pharmaceutical Co., Ltd.,

329 Chugai Pharmaceutical Co., Ltd., AstraZeneca K.K., and Eli Lilly Japan K.K.

330 Eriko Satomi received honoraria from Shionogi & Co. Ltd. Masayuki Takeda

331 received honoraria from Chugai Pharmaceutical Co., Ltd.; AstraZeneca K.K.;

332 Novartis Pharma K.K.; Ono Pharmaceutical Co., Ltd.; and Bayer. Takako

333 Eguchi Nakajima received research funding from KBBM, Inc. and Takeda

334 Pharmaceutical Co., Ltd. Junichi Nishimura received honoraria from Taiho

335 Pharmaceutical Co. Ltd. Narikazu Boku received honoraria from Ono

336 Pharmaceutical Co., Ltd., Bristol Myers Squibb, Daiichi Sankyo Co., Ltd.,

337 Taiho Pharmaceutical Co., Ltd., and Eli Lilly Japan K.K. Koji Matsumoto

338 received honoraria from MSD K.K., Kyowa Kirin Co., Ltd., and Chugai

339 Pharmaceutical Co., Ltd. as well as research funding from Daiichi Sankyo

340 Co., Ltd., MSD K.K., Gilead Sciences, Inc., and Eli Lilly Japan K.K.

341 Nobuyuki Yamamoto received honoraria from MSD K.K., Accuray Japan

342 K.K., AstraZeneca K.K., Abbvie Inc., Amgen Inc., Ono Pharmaceutical Co.,

343 Ltd., Guardant Health Japan Corp., Daiichi Sankyo Co., Ltd., Taiho

344 Pharmaceutical Co., Ltd., Takeda Pharmaceutical Co., Ltd., Chugai

345 Pharmaceutical Co., Ltd., Chugai Foundation for Innovative Drug Discovery

346 Science, Lao Tsumura Co., Ltd., Terumo Corporation, Eli Lilly Japan K.K.,

347 Nippon Kayaku Co., Ltd., Novartis AG, Pfizer Global Supply Japan Inc.,

348 Merck Biopharma Co., Ltd, Pfizer Global Supply Japan Inc., Merck

349 Biopharma Co., Ltd., Janssen Pharmaceutical K.K., and USACO Corporation,

350 as well as legal fees in case of lawsuit from Taiho Pharmaceutical Co., Ltd.,

351 Boehringer Ingelheim Japan, Chugai Pharmaceutical Co., Ltd., Kyowa Kirin

352 Co., Ltd., Nippon Kayaku Co., Ltd., Prime Research Institute for Medical

353 RWD, Inc., AstraZeneca K.K., and A2 Healthcare Corporation. The authors

354 declare no conflicts of interest.

355

356 **References**

- 357 1. Iihara H, Abe M, Wada M, et al. (2024) 2023 Japan Society of Clinical

358 Oncology Clinical practice guidelines update for antiemesis. Int J Clin

359 Oncol [Online ahead of print] 29:873–888. doi: 10.1007/s10147-024-

360 02535-x
- 361 2. Hesketh PJ, Kris MG, Basch E, et al. (2020) Antiemetics: ASCO

362 guideline update. J Clin Oncol 38:2782–2797
- 363 3. Herrstedt J, Celio L, Hesketh PJ, et al. (2023) 2023 updated

364 MASCC/ESMO consensus recommendations: prevention of nausea and

365 vomiting following high-emetic-risk antineoplastic agents. Support Care
366 Cancer 32:47

367 4. National Comprehensive Cancer Network. Antiemesis, version 1.2024.
368 https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf.
369 Accessed April 2024

370 5. Vardy J, Chiew KS, Galica J, et al. (2006) Side effects associated with
371 the use of dexamethasone for prophylaxis of delayed emesis after
372 moderately emetogenic chemotherapy. Br J Cancer 94:1011–1015

- 373 6. Nakamura M, Ishiguro A, Muranaka T, et al. (2017) A prospective
374 observational study on effect of short-term periodic steroid
375 premedication on bone metabolism in gastrointestinal cancer
376 (ESPRESSO-01). *Oncologist* 22:592–600
- 377 7. Jeong Y, Han HS, Lee HD, et al. (2016) A pilot study evaluating steroid-
378 induced diabetes after antiemetic dexamethasone therapy in
379 chemotherapy-treated cancer patients. *Cancer Res Treat* 48:1429–1437
- 380 8. Celio L, Bonizzoni E, Zattarin E, et al. (2019) Impact of dexamethasone-
381 sparing regimens on delayed nausea caused by moderately or highly

382 emetogenic chemotherapy: a meta-analysis of randomised evidence.

383 BMC Cance 19:1268

384 9. Scotté F, Schwartzberg L, Iihara H, et al. (2023) 2023 updated

385 MASCC/ESMO Consensus recommendations: prevention of nausea and

386 vomiting following moderately emetic risk antineoplastic agents.

387 Support Care Cancer 32:45

388 10. Kojimahara N, Nakayama T, Morizane T, et al. eds. (2017) Minds manual

389 for guideline development 2017. Japan Council for Quality Health Care,

390 Tokyo

- 391 11. Shea BJ, Hamel C, Wells GA, et al. (2009) AMSTAR is a reliable and
392 valid measurement tool to assess the methodological quality of
393 systematic reviews. *J Clin Epidemiol* 62:1013–1020
- 394 12. Jaeschke R, Guyatt GH, Dellinger P, et al. (2008) Use of GRADE grid to
395 reach decisions on clinical practice guidelines when consensus is elusive.
396 *BMJ* 337: a744
- 397 13. Ito Y, Tsuda T, Minatogawa H, et al. (2018) Placebo-controlled, double-
398 blinded phase III study comparing dexamethasone on day 1 with
399 dexamethasone on days 1 to 3 with combined neurokinin-1 receptor

400 antagonist and palonosetron in high-emetogenic chemotherapy. J Clin
401 Oncol 36:1000–1006

402 14. Kosaka Y, Tanino H, Sengoku N, et al. (2016) Phase II randomized,
403 controlled trial of 1 day versus 3 days of dexamethasone combined with
404 palonosetron and aprepitant to prevent nausea and vomiting in Japanese
405 breast cancer patients receiving anthracycline-based chemotherapy.
406 Support Care Cancer 24:1405–1411

407 15. Minatogawa H, Izawa N, Shimomura K, et al. (2024) Dexamethasone-
408 sparing on days 2–4 with combined palonosetron, neurokinin-1 receptor

409 antagonist, and olanzapine in cisplatin: a randomized phase III trial

410 (SPARED Trial). Br J Cancer 130:224–232

411 16. Celio L, Cortinovis D, Cogoni AA, et al. (2021) Dexamethasone-sparing

412 regimens with oral netupitant and palonosetron for the prevention of

413 emesis caused by high-dose cisplatin: A randomized noninferiority study.

414 Oncologist 26:e1854–e1861

415 17. Celio L, Bonizzoni E, Montani E, et al. (2022) Efficacy of the

416 dexamethasone-sparing triplet regimen for preventing cisplatin-induced

417 emesis: a combined analysis. Future Oncol 18:3389–3397

- 418 18. Zhang L, Lu S, Feng J, et al. (2018) A randomized phase III study
419 evaluating the efficacy of single-dose NEPA, a fixed antiemetic
420 combination of netupitant and palonosetron, versus an aprepitant
421 regimen for prevention of chemotherapy-induced nausea and vomiting
422 (CINV) in patients receiving highly emetogenic chemotherapy (HEC).
423 Ann Oncol 29:452–458
- 424 19. Hata A, Okamoto I, Inui N, et al. (2022) Randomized, double-blind,
425 Phase III study of fosnetupitant versus fosaprepitant for prevention of

426 highly emetogenic chemotherapy-induced nausea and vomiting:

427 CONSOLE. J Clin Oncol 40:180–188

428 20. Hashimoto H, Abe M, Tokuyama O, et al. (2020) Olanzapine 5 mg plus

429 standard antiemetic therapy for the prevention of chemotherapy-induced

430 nausea and vomiting (J-FORCE): a multicentre, randomised, double-

431 blind, placebo-controlled, phase 3 trial. Lancet Oncol 21:242–249

432

433 Table.1 Characteristics of randomized controlled studies included in the meta-

434 analysis

Characteristics	Author, year			
	Kosaka, 2016		Ito, 2018	
Study design	Single-blind, Single-center, Placebo-controlled, Superiority		Double-blind, Multicenter, Placebo-controlled, Non-inferiority	
NK ₁ RA	APR 125 mg po on day 1 + APR 80 mg po on days 2-3		APR 125 mg po on day 1 + APR 80 mg po on days 2-3 or FosAPR 150 mg iv on day 1	
5-HT ₃ RA	Palonosetron 0.75 mg div on day 1			
DEX	DEX 12 mg iv on day 1 1) iv or po placebo on days 2-3, 2) iv or po DEX 8 mg on days 2-3			
No. of patients	1) 39 2) 41		1) 200 2) 196	
Age, median (range)	1) 52.6 (37–67) 2) 53.5 (35–76)		1) 54.1 (27–78) 2) 55.0 (24–79)	

Female, n (%)	1) 39 (100)	2) 41 (100)	1) 163 (81.5)	2) 157 (80.1)
Primary tumor, n (%)				
Breast	1) 39 (100)	2) 41 (100)	1) 155 (77.5)	2) 150 (76.5)
Upper gastrointestinal	-	-	1) 34 (17.0)	2) 34 (17.3)
Lung	-	-	1) 10 (5)	2) 7 (3.6)
Other	-	-	1) 1 (0.5)	2) 5 (2.6)
Chemotherapy, n (%)				
AC-based HEC	1) 39 (100)	2) 41 (100)	1) 155 (77.5)	2) 151 (77.0)
CDDP-based HEC	-	-	1) 45 (23.5)	2) 45 (23.0)

435 Abbreviations: NK₁RA, neurokinin-1 receptor antagonists; APR, aprepitant;

436 FosAPR, fosaprepitant; po, per oral; iv, intravenous; 5-HT₃RA, second-

437 generation serotonin receptor antagonists; DEX, dexamethasone; AC,

438 anthracycline-cyclophosphamide combination; CDDP, cisplatin; HEC,

439 highly emetogenic chemotherapy

440 **Figure legends**

441 **Fig. 1** Modified PRISMA flow diagram of the literature search and study

442 selection process

443 Each study was included in the meta-analysis of delayed CR (*1) and delayed

444 CC (*2).

445 PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-

446 analysis; CR, complete response; CC, complete control

447

448 **Fig. 2** A forest plot of the risk differences of delayed CR comparing DEX

449 sparing and control study arms for each study

450 DEX, dexamethasone; CR, complete response; CI, confidence interval; RD,

451 risk difference; SE, standard error

452

453 **Fig. 3** A forest plot of the risk differences of delayed CC comparing DEX

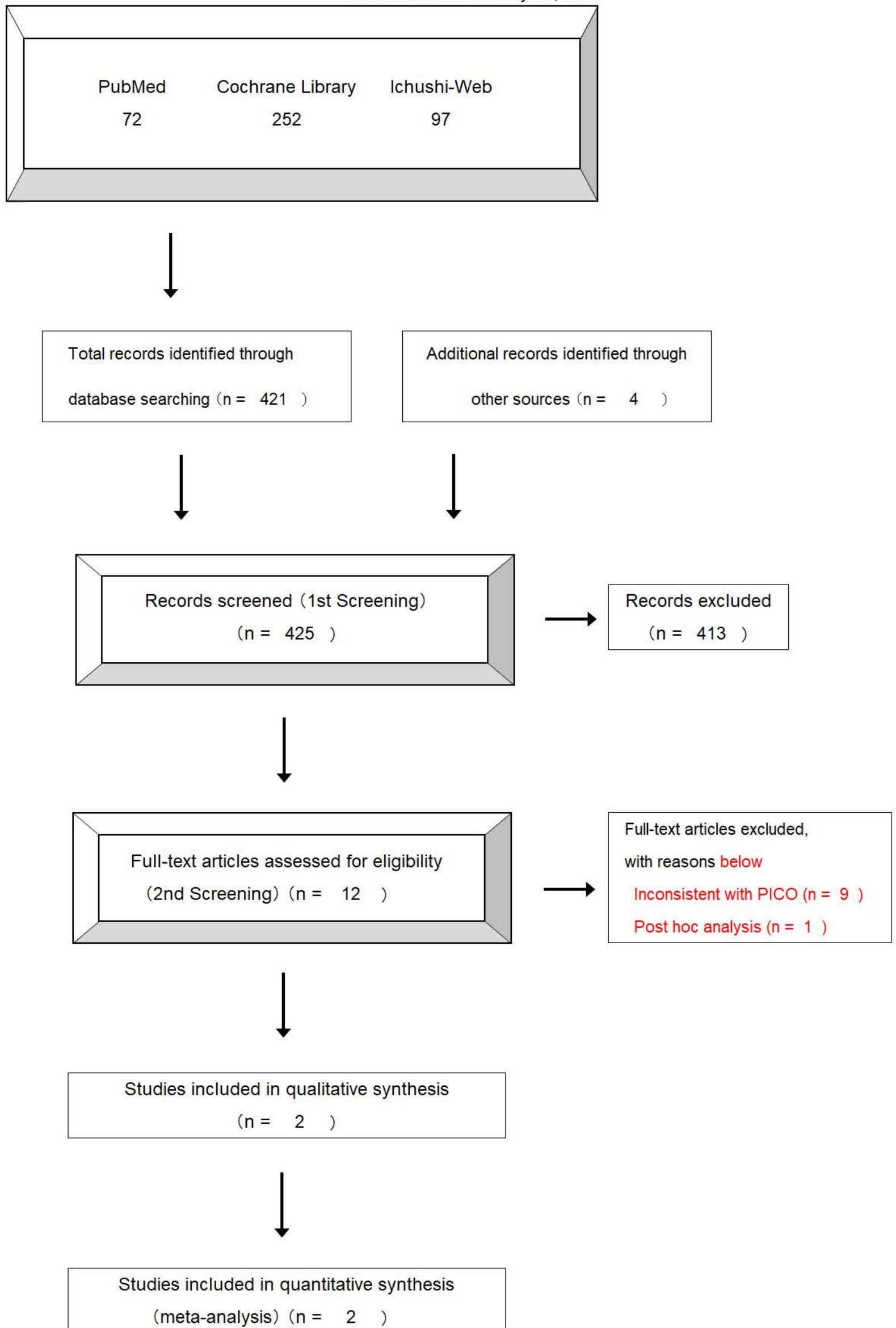
454 sparing and control study arms for each study

455 DEX, dexamethasone; CC, complete control; CI, confidence interval; RD,

456 risk difference; SE, standard error

Fig. 1

Date of search: February 25, 2021



Characteristics	Author, year			
	Kosaka, 2016		Ito, 2018	
Study design	Single-blind, Single-center, Placebo-controlled, Superiority		Double-blind, Multicenter, Placebo-controlled, Non-inferiority	
NK ₁ RA	APR 125 mg po on day 1 + APR 80 mg po on days 2-3		APR 125 mg po on day 1 + APR 80 mg po on days 2-3 or FosAPR 150 mg iv on day 1	
5-HT ₃ RA	Palonosetron 0.75 mg div on day 1			
DEX	DEX 12 mg iv on day 1 1) iv or po placebo on days 2-3, 2) iv or po DEX 8 mg on days 2-3			
No. of patients	1) 39	2) 41	1) 200	2) 196
Age, median (range)	1) 52.6 (37–67)	2) 53.5 (35–76)	1) 54.1 (27-78)	2) 55.0 (24-79)

Female, n (%)	1) 39 (100)	2) 41 (100)	1) 163 (81.5)	2) 157 (80.1)
Primary tumor, n (%)				
Breast	1) 39 (100)	2) 41 (100)	1) 155 (77.5)	2) 150 (76.5)
Upper gastrointestinal	-	-	1) 34 (17.0)	2) 34 (17.3)
Lung	-	-	1) 10 (5)	2) 7 (3.6)
Other	-	-	1) 1 (0.5)	2) 5 (2.6)
Chemotherapy, n (%)				
AC-based HEC	1) 39 (100)	2) 41 (100)	1) 155 (77.5)	2) 151 (77.0)
CDDP-based HEC	-	-	1) 45 (23.5)	2) 45 (23.0)

