One-Day Versus Three-Day Dexamethasone in Combination with Palonosetron for the Prevention of Chemotherapy-Induced Nausea and Vomiting: A Systematic Review and Individual Patient Data-Based Meta-Analysis

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Nausea • Vomiting • Chemotherapy-induced nausea and vomiting • Moderately emetogenic chemotherapy • Dexamethasone • Palonosetron

ABSTRACT

Background. A dexamethasone-sparing regimen consisting of palonosetron plus 1-day dexamethasone for the prevention of chemotherapy-induced nausea and vomiting (CINV) has been studied previously. Here, we evaluate the noninferiority of the dexamethasone-sparing regimen in overall antiemetic control using a meta-analysis based on individual patient data (IPD).

Materials and Methods. We conducted a systematic review for randomized trials reporting CINV outcomes for the comparison of palonosetron plus 1-day dexamethasone (d1 arm) versus the same regimen followed by dexamethasone on days 2–3 after chemotherapy (d3 arm) in chemotherapy-naïve adult patients undergoing either moderately emetogenic chemotherapy (MEC) or anthracycline plus cyclophosphamide (AC)-containing chemotherapy. PubMed and MEDLINE were searched electronically. A manual search was also conducted. The primary endpoint was complete response (CR; no emesis and no rescue medication) in the overall 5-day study period. The noninferiority margin was set at −8.0% (d1 arm−d3 arm).

Results. Five studies (n = 1,194) were eligible for analysis and all IPD was collected. In the overall study period, the d1 arm showed noninferiority to the d3 arm for CR as well as complete control (pooled risk difference in CR rate −1.5%, 95% confidence interval [CI] −7.1 to 4.0%, I² = 0%; in complete control rate −2.4%, 95% CI −7.7 to 2.9%, I² = 0%). There was no significant interaction between dexamethasone regimen and risk factors (type of chemotherapy, sex, age, and alcohol consumption).

Conclusion. This IPD meta-analysis indicates that the dexamethasone-sparing regimen is not associated with a significant loss in overall antiemetic control in patients undergoing MEC or AC-containing chemotherapy, irrespective of known risk factors for CINV. The Oncologist 2019;24:1593–1600

Implications for Practice: Although dexamethasone in combination with other antiemetic agents has been used to prevent chemotherapy-induced nausea and vomiting (CINV), it is of clinical importance to minimize total dose of dexamethasone in patients undergoing multiple cycles of emetogenic chemotherapy. This individual-patient-data meta-analysis from five

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) is the most common nonhematological toxicity associated with the use of cytotoxic chemotherapy drugs, with incidence rates ranging around 70%–80% [1–3]. The optimal prevention of CINV remains a major clinical issue, which is directly related to adherence with chemotherapy and maintaining patient quality of life [1]. The guidelines developed by international societies recommend prophylaxis for CINV based on the emetogenicity of individual antineoplastic agents, which is classified into four categories as follows: highly emetogenic chemotherapy (HEC), moderately emetogenic chemotherapy (MEC), low emetogenic chemotherapy, and minimally emetogenic chemotherapy [4–8]. Whereas anthracyclines and cyclophosphamide are categorized as MEC, the combination of an anthracycline and cyclophosphamide (AC) has been recently reclassified as HEC. In the MEC setting, the cornerstone of antiemetic prophylaxis has long been a two-drug regimen consisting of a 5-hydroxytryptamine-3 (5-HT3) receptor antagonist and multiple-day dexamethasone for the prevention of acute and delayed CINV [7, 9].

Palonosetron, a second-generation 5-HT3 receptor antagonist, is superior to the first-generation antagonists in efficacy and safety, having greater binding affinity for the 5-HT3 receptor and a longer elimination half-life [10]. Additionally, palonosetron is the only agent in the class that is approved for the prevention of delayed CINV after MEC [10]. Dexamethasone synergistically enhances the antiemetic efficacy of 5-HT3 receptor antagonists [11]. Although dexamethasone in combination with other antiemetic agents is recognized to be safe [12, 13], dexamethasone has been shown to cause moderate-to-severe adverse effects, such as insomnia, gastrointestinal symptoms, agitation, increased appetite, and weight gain, in patients receiving the steroid for delayed CINV [14]. Besides, dexamethasone could potentially deteriorate a patient’s condition (e.g., diabetes, osteopenia/osteoporosis, and cataracts). Accordingly, it is of clinical importance to minimize the total dose of prophylactic dexamethasone in patients undergoing multiple cycles of emetogenic chemotherapy.

Aapro et al. [15] reported that a dexamethasone-sparing regimen consisting of palonosetron plus single-dose dexamethasone (d1 arm) would not be inferior to the same regimen followed by additional dexamethasone doses on days 2 to 3 after chemotherapy initiation (d3 arm) regarding complete response (CR; no emesis and no rescue medication) rate. Two subsequent randomized phase III studies were performed with a similar objective, which also showed the noninferiority of the dexamethasone d1 arm for the prevention of CINV in patients undergoing a broad range of MEC regimens [16, 17]. However, because of a wide range of noninferiority margin (15%) and limited number of subjects in these three studies, evidence for the noninferiority of the dexamethasone d1 arm in patients with risk factors for CINV is insufficient. In addition, it is unclear whether well-known risk factors for CINV, such as female sex, younger age, and history of alcohol consumption [11], modify the treatment effect on the antiemetic outcome [15–17].

We therefore performed a meta-analysis of individual patient data (IPD) gathered from eligible studies identified in a systematic review of randomized control trials that had assessed the effect of reduction in dexamethasone total dose on CINV onset in patients receiving a prophylactic regimen of palonosetron and dexamethasone. We aimed to comprehensively evaluate any difference in CR rate and other antiemetic outcomes between the d1 arm and d3 arm as well as to explore any interaction between antiemetic regimen and predefined risk factors for CINV.

Materials and Methods

Study Protocol

First, we formed a meta-analysis research group and contacted the principal investigators of the three aforementioned studies [15–17]. A protocol stipulating the research objective, selection criteria, search method, and analysis method was drawn up, and a systematic review was performed. The institutional review board at the University of Tokyo approved the study protocol (No. 11539).

Eligible studies were defined as randomized control trials of anti-CINV palonosetron and dexamethasone combination therapies in chemotherapy-naïve patients aged 18 years or above with malignant tumors in which regimens with and without dexamethasone dose reduction were compared. Considering the approval date for palonosetron, studies performed in or after the year of 2000 were regarded as eligible for inclusion. Studies involving nonchemotherapy treatments, such as radiotherapy and immunotherapy, were excluded. The PubMed and Ovid MEDLINE databases were searched electronically. Each database was searched for studies between January 2000 and November 2016 using the search filters without language restrictions (supplemental online Table 1).

In the event that any reviews or meta-analyses were included in the search results, further searches were made to determine whether additional studies were eligible while checking the cited reports. Specialists in the research group also checked for any relevant studies that were not targeted in the electronic search. For studies with multiple publications, or where there was an overlap in the patients studied, the original study in question was included. All retrieved studies were refined and assessed independently for eligibility with the title and/or abstracts and the full text publication by two reviewers (one of whom was the author). We contacted the principal authors of the reports for
each eligible study and acquired IPD from each study. All data were centrally reanalyzed and checked for inconsistencies.

**Collected Data**

Sex, age, primary tumor, chemotherapy regimen, performance status (PS), and alcohol consumption habit were considered as patient demographic characteristics. The presence or absence of both CR (no emesis and no rescue medication) and complete control (CC; defined as no emesis, no rescue medication, and no more than mild nausea) during the acute (within 24 hours of chemotherapy initiation), delayed (days 2–5 after chemotherapy initiation), and overall (days 1–5) study periods were considered as outcome variables. Those outcomes were based on a patient diary used to document the date and time of emetic episodes and use of rescue medication, as well as severity of nausea with a four-point categorical scale (none; mild; moderate; severe) or an alternative assessment tool.

**Endpoints**

The primary efficacy endpoint was CR during the overall study period. Secondary endpoints were CR during the acute and delayed periods as well as CC during all study periods. In addition to the whole-population analyses, subgroup analyses were performed for the following risk factors: type of chemotherapy (AC-based HEC vs. MEC), age (younger than 60 years vs. 60 years or older), sex (male vs. female), habitual alcohol consumption (yes vs. no), and Eastern Cooperative Oncology Group PS (0 vs. 1 or higher).

**Statistical Analyses**

Data on the designs and characteristics of enrolled patients in the eligible studies were pooled. Continuous variables were summarized by mean and SD, and categorical variables were summarized by the number and proportion of subjects. Common risk differences of the primary and secondary endpoints were estimated through a one-stage fixed effect model [18]. Heterogeneity on the risk difference between trials was assessed through the interaction test between study and treatment in the fixed effect model. Heterogeneity was also quantitatively assessed using the $I^2$ statistic. Subgroup analyses were then performed by predefined risk factors, examining the interaction between each factor and treatment effects.

Ioannidis et al. showed that the pooled risk difference of dexamethasone compared with placebo for CR was 16% (95% confidence interval [CI], 13%–19%) for the acute phase and 16% for the delayed phase [19]. In our analysis, the noninferiority margin for the primary endpoint was set to 8.0% (half of the 16% risk difference) of the between-arm difference. Noninferiority was demonstrated when the lower boundary of the 95% CI of the risk difference was greater than the preset threshold (−8%). Heterogeneity was considered statistically significant in interaction testing when the $p$ value was .10 or lower.

The analyses were performed with SAS statistical software (version 9.4; SAS Institute, Cary, NC). Forest plots were constructed with STATA statistical software (version 14.2; STATA Corp LP, College Station, TX).

**RESULTS**

**Listing of Eligible Studies**

A total of five studies satisfied the eligibility criteria in the systematic review. All of these studies were phase II or III randomized controlled trials and had been published in peer-reviewed journals. The PRISMA study selection diagram is shown in Figure 1. IPD were acquired from each of the five studies after contacting the principal investigator. An overview and characterization of each study along with patient characteristics is presented in Table 1. Twenty ineligible trials along with their reasons for exclusion are presented in supplemental online Table 2.

The eligible studies were as follows: a study of patients receiving AC-based HEC performed by Aapro et al. (Aapro study) [15]; a study of patients treated with a broad range of MEC regimens, including AC-based HEC, performed by Celio et al. (Celio study) [16]; a study of patients receiving only MEC regimens performed by Komatsu et al. (Komatsu study) [17]; a study of carboplatin-containing MEC performed by Furukawa et al. (Furukawa study) [20]; and a study of patients treated with AC-based HEC performed by Kosaka et al. (Kosaka study) [21]. These five studies yielded an analysis population of 1,194 subjects. The subjects in the Aapro, Furukawa, and Kosaka studies were women with either breast cancer or gynecologic cancer. The subjects in the other two studies were chemotherapy-naïve patients with a broad range of solid tumors. The intravenous dose of palonosetron was 0.25 mg in the Aapro and Celio studies, whereas the approved dose of palonosetron 0.75 mg was used in the
other three studies. Dexamethasone dosage and administration varied widely between the studies because of the several different settings of CINV; however, there were few major differences. No bias in any patient characteristics was noted between the treatment arms in each study.

Primary Endpoint (CR Rate) Evaluation
The risk difference between the two treatments for overall CR rate (primary efficacy endpoint) was $-1.5\%$ (95% CI, $-7.1\%$ to $4.0\%$; Fig. 2), and the noninferiority of the dexamethasone-sparing regimen was demonstrated in this analysis. Heterogeneity testing yielded $p = .892$ and $I^2 = 0\%$, and interstudy heterogeneity could not be demonstrated. The risk differences for acute-phase and delayed-phase CR rates were $0.4\%$ (95% CI, $-3.4\%$ to $4.2\%$) and $-2.3\%$ (95% CI, $-7.4\%$ to $2.9\%$), respectively, demonstrating noninferiority between treatments (Table 2). No statistically significant heterogeneity across the studies was noted among overall, acute-phase, and delayed-phase CR rates.

CC Rate Evaluation
In the Aapro study, daily nausea ratings were assessed by visual analog scale (VAS); 0 mm “no nausea” and 100 mm “as bad as it could be,” where complete control (CC) was defined as no emesis, no rescue medication, and no more than mild nausea (a VAS <25 mm). In the Furukawa study, CC was defined as no emetic episodes, no use of rescue medication, and no significant nausea (a score by Multinational Association for�
Table 2. Risk differences for CR rates in each study period

| Study               | Overall-phase CR | Acute-phase CR | Delayed-phase CR |
|---------------------|------------------|----------------|------------------|
|                     | d1 arm, n (%)³   | d3 arm, n (%)³ | d1 arm, n (%)³   | d3 arm, n (%)³ | d1 arm, n (%)³   | d3 arm, n (%)³ |
| Aapro et al. [15]   | 81 (53.6)        | 80 (53.7)      | −0.1 (−11.3 to 11.2) | 105 (69.5) | 102 (68.5)      | 1.1 (−9.4 to 11.6) |
| Cello et al. [16]   | 109 (66.9)       | 113 (70.2)     | −3.3 (−13.4 to 6.8) | 144 (88.3) | 135 (83.9)      | 4.5 (−3.0 to 12.0) |
| Furukawa et al. [20]| 29 (67.4)        | 30 (76.9)      | −9.5 (−28.7 to 9.8) | 41 (95.4) | 37 (94.9)       | 0.5 (−8.9 to 9.8) |
| Komatsu et al. [17] | 100 (64.9)       | 98 (63.6)      | 1.3 (−9.4 to 12.0) | 141 (91.6) | 142 (92.2)      | −0.7 (−6.8 to 5.5) |
| Kosaka et al. [21]  | 32 (82.1)        | 34 (82.9)      | −0.9 (−17.5 to 15.8)| 32 (82.1) | 38 (92.7)       | −10.6 (−25.1 to 3.8) |
| All(³)              | −1.5 (−7.1 to 4.0)³, | 0.4 (−3.4 to 4.2)³, | −2.3 (−7.4 to 2.9)³, |

Overall, days 1–5 after chemotherapy. Acute phase, 0–24 hours after chemotherapy; Delayed phase, days 2–5 after chemotherapy.
³d1 arm: palonosetron plus 1-day dexamethasone.
³d3 arm: palonosetron plus 3-day dexamethasone.
³Overall combined (pooled) result with fixed-effect model.

Table 3. Risk differences for CC rates in each study period

| Study               | Overall-phase CC | Acute-phase CC | Delayed-phase CC |
|---------------------|------------------|----------------|------------------|
|                     | d1 arm, n (%)³   | d3 arm, n (%)³ | d1 arm, n (%)³   | d3 arm, n (%)³ | d1 arm, n (%)³   | d3 arm, n (%)³ |
| Aapro et al. [15]   | 73 (48.3)        | 73 (49.0)      | −0.7 (−12.0 to 10.7)  | 103 (68.2) | 96 (64.4)       | 3.8 (−6.9 to 14.5)  |
| Cello et al. [16]   | 105 (64.4)       | 109 (67.7)     | −3.3 (−13.6 to 7.0) | 142 (87.1) | 132 (82.0)      | 5.1 (−2.7 to 13.0)  |
| Furukawa et al. [20]| 28 (71.8)        | 28 (65.1)      | −6.7 (−26.7 to 13.4) | 39 (90.7) | 37 (94.9)       | −4.2 (−15.3 to 6.9) |
| Komatsu et al. [17] | 98 (63.6)        | 95 (61.7)      | 1.9 (−8.9 to 12.7) | 141 (91.6) | 142 (92.2)      | −0.6 (−6.7 to 5.5)  |
| Kosaka et al. [21]  | 24 (61.5)        | 20 (48.8)      | 12.8 (−8.9 to 34.4) | 28 (71.8) | 26 (63.4)       | 8.4 (−12.0 to 28.8) |
| All(³)              | −0.3 (−6.0 to 5.5)³, | 1.4 (−2.6 to 5.4)³, | −3.9 (−9.5 to 1.6)³, |

Overall, days 1–5 after chemotherapy. Acute phase, 0–24 hours after chemotherapy; Delayed phase, days 2–5 after chemotherapy.
³d1 arm: palonosetron plus 1-day dexamethasone.
³d3 arm: palonosetron plus 3-day dexamethasone.
³Overall combined (pooled) result with fixed-effect model.

Abbreviations: CI, confidence interval; CC, complete control; RD, risk difference.
The present IPD-based meta-analysis demonstrated the noninferiority of the dexamethasone-sparing regimen for both CR and CC with a margin of 8.0% for the prevention of CINV in patients undergoing either AC-based HEC or MEC regimens. We also explored the impact of predefined risk factors for CINV on CR rates between the two antiemetic treatments. The subgroup analyses showed no major difference in antiemetic effect between the regimens during the overall study period. The results of this study provide strong evidence for a prophylactic regimen of palonosetron and dexamethasone for the prophylaxis of acute nausea and vomiting, the 2016 MASCC guidelines explored a lack of evidence for the use of dexamethasone without the loss of antiemetic efficacy, at least when longer-acting 5-HT3 receptor antagonists are used.

Although previous Multinational Association of Supportive Care in Cancer (MASCC)/European Society for Medical Oncology (ESMO) guidelines (the 2010 MASCC guidelines) preferred palonosetron plus dexamethasone for the prophylaxis of acute nausea and vomiting, the 2016 MASCC guidelines explored a lack of evidence for the use of dexamethasone for days 2–3 routinely for prophylaxis for delayed CINV until their revision [7, 8]. To the best of our knowledge, there are no trials of the dexamethasone-sparing strategy in older generation than palonosetron because their meta-analysis was conducted in 2000, before palonosetron was approved in 2003. Cello et al. [10] conducted a narrative review of the evidence about the efficacy and safety of palonosetron, but they did not examine the necessity for concomitant dexamethasone. The present study is the first to assess the clinical relevance of the dexamethasone-sparing strategy in a systematic review with IPD meta-analysis.

**Table 4. Patient characteristic subgroup analysis and interaction for overall CR**

| Characteristics         | d1 arm** | d3 arm*** | Heterogeneity, p value | Interaction, p value |
|-------------------------|----------|----------|------------------------|---------------------|
|                         | n        | CR, n (%)| n                      | RD, % (95% CI)      |
| Sex                     | n        | CR, n (%)| n                      | RD, % (95% CI)      |
| Men                     | 150      | 111 (74.0) | 139                    | 105 (75.5)          | −2.3 (−12.2 to 7.7) | .276 |
| Women                   | 400      | 240 (60.0) | 405                    | 250 (61.7)          | −1.8 (−8.3 to 4.8) | .947 |
| Age, years              |          |          |                        |                     |                     |     |
| <60                     | 293      | 167 (57.0) | 281                    | 174 (61.9)          | −4.8 (−12.6 to 3.1) | .635 |
| ≥60                     | 257      | 184 (71.6) | 263                    | 181 (68.8)          | 2.3 (−5.3 to 9.9)   | .431 |
| Chemotherapy regimen    |          |          |                        |                     |                     |     |
| AC-based HEC            | 229      | 133 (58.1) | 238                    | 145 (60.9)          | −2.5 (−11.0 to 6.0) | .532 |
| MEC                     | 321      | 218 (67.9) | 306                    | 210 (68.6)          | −1.1 (−8.3 to 6.2)  | .630 |
| Habitual alcohol consump. |          |          |                        |                     |                     |     |
| Yes                     | 148      | 102 (68.9) | 147                    | 111 (75.5)          | −5.6 (−15.8 to 4.6) | .976 |
| No                      | 367      | 226 (61.6) | 363                    | 226 (62.3)          | −0.7 (−7.5 to 6.1)  | .743 |

Overall combined (pooled) result with fixed-effect model. Overall CR was evaluated during the overall study period (days 1–5 after chemotherapy initiation).

**Table 3.** Characteristics of patients included in each study.

| Characteristics         | Study 1 | Study 2 | Study 3 | Total |
|-------------------------|---------|---------|---------|-------|
| Chemotherapy regimen    | AC-based HEC | MEC, moderately emetogenic chemotherapy | AC-based HEC | AC-based HEC, MEC, moderately emetogenic chemotherapy |
| Patient characteristics | Men     | Women   | Men     | Women |
| Age, years              | <60     | ≥60     | <60     | ≥60   |
| Alcohol consumption     | Yes     | No      | Yes     | No    |

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Subgroup analyses revealed no significant interaction between treatment and sex, age category, alcohol consumption habit, or chemotherapy regimen (AC-based HEC vs. MEC). However, the study by Komatsu et al. found disparity between older and younger age subgroups in risk difference for CR rate [17]. Therefore, dexamethasone dose could be reduced irrespective of whether the patient is younger or older than 60 years. In addition to the risk factors discussed above (emergent properties of chemotherapy, sex, age, and alcohol consumption habit), other known risk factors should be noted, including rapid 5-HT3 receptor antagonist metabolism, 5-HT3 receptor polymorphism, history of motion sickness, anxiety, and fatigue [10]. We acknowledge that these other risk factors were not taken into consideration in the present study.

Effective approaches to reduce patients’ exposure to steroids remain among the hot topics in clinical research on CINV. Recent evidences from prospective studies highlighted a potentially detrimental impact of short-term prophylactic dexamethasone in patients undergoing consecutive courses of emetogenic chemotherapy [22, 23]. Aapro et al. compared the efficacy of palonosetron when administered alone or in combination with 1-day dexamethasone, in post hoc analyses of two studies on CINV in patients undergoing MEC; they reported that the proportion of nausea was lower in patients treated with the 1-day dexamethasone regimen over a 5-day period [24, 25]. However, it is difficult to clearly interpret these results because it involved a straightforward comparison of two studies without adopting appropriate endpoints, such as CR and CC, which were assessed in the present study. It is worth noting that the efficacy of a dexamethasone-free prophylaxis with palonosetron for patients undergoing MEC regimens will be assessed in a noninferiority trial that is in progress in Japan [26].

The present study has some limitations. Current guidelines recommend a three-drug prophylaxis consisting of a 5-HT3 receptor antagonist, dexamethasone, and a neurokinin-1 receptor antagonist (NK-1RA) for prevention of CINV caused by AC-based chemotherapy [8, 9, 27]; however, the combination of AC, currently classified as HEC [7–9, 27], was included in the MEC category in the period when the five studies were conducted. In that period, the relevant guidelines had been updated or revised multiple times [5–8]. In the present study, only the Kosaka study evaluated the efficacy of the dexamethasone-sparing strategy in patients with breast cancer treated with AC and receiving three-drug prophylaxis for CINV [21]. Nevertheless, the study findings are consistent with the results of a recently published phase III trial that demonstrated a noninferiority difference between the three-drug, dexamethasone-sparing regimen and the control arm for the prevention of CINV caused by HEC regimens [28]. Approximately 400 patients were included in the study, but the majority (77%) of them were patients with breast cancer treated with AC. Also, international antiemetic guidelines still recommend a two-drug prophylaxis consisting of palonosetron plus dexamethasone in patients with breast cancer treated with AC when an NK-1RA is not available [8]. Our results support that the dexamethasone-sparing regimen should represent the first-choice prophylaxis for patients who do not receive NK-1RA. Moreover, we could not carry out any clinically meaningful analysis of tolerability for the dexamethasone-sparing regimen as the eligible studies provided only sparse information to reliably assess any between-arm differences in the incidence of dexamethasone-related side effects.

**Conclusion**

The present IPD meta-analysis shows that the dexamethasone-sparing strategy does not result in any significant loss in overall antiemetic control and indicates that multiple-day dexamethasone dosing is an unnecessary component of antiemetic prophylaxis with palonosetron before the start of chemotherapy in patients undergoing single-day MEC or AC-based regimens. Our findings thus help physicians minimize use of the steroid and further reduce the burden of dexamethasone-related side effects in patients undergoing multiple consecutive courses of emetogenic chemotherapy.

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**Disclosures**

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