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Symptom Management and Supportive Care

Metoclopramide, Dexamethasone, or Palonosetron for Prevention of Delayed Chemotherapy-Induced Nausea and Vomiting After Moderately Emetogenic Chemotherapy (MEDEA): A Randomized, Phase III, Noninferiority Trial

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

Key Words. Metoclopramide • Dexamethasone • Palonosetron • Vomiting • Nausea • Moderately emetogenic chemotherapy

Abstract

Background. For the prevention of chemotherapy-induced nausea and vomiting (CINV) during the delayed phase (24–120 hours) after moderately emetogenic chemotherapy (MEC), the use of 3-day dexamethasone (DEX) is often recommended. This study compared the efficacy and safety of two DEX-sparing regimens with 3-day DEX, focusing on delayed nausea.

Patients and Methods. This open-label, randomized, phase III study was designed to demonstrate noninferiority of two DEX-sparing regimens: ondansetron + DEX on day 1 + metoclopramide on days 2–3 (MCP arm), and palonosetron + DEX on day 1 (PAL arm) versus ondansetron on day 1 + DEX on days 1–3 (DEX arm) in chemotherapy-naïve patients receiving MEC. Primary efficacy endpoint was total control (TC; no emetic episodes, no use of rescue medication, no nausea) in the delayed phase. Noninferiority was defined as a lower 95% CI greater than the noninferiority margin set at −20%. Secondary endpoints included no vomiting, no rescue medication, no (significant) nausea, impact of CINV on quality of life, and antiemetics-associated side effects.

Results. Treatment arms were comparable for 189 patients analyzed: predominantly male (55.7%), median age 65.0 years, colorectal cancer (85.7%), and oxaliplatin-based chemotherapy (81.5%). MCP demonstrated noninferiority to DEX for delayed TC (MCP 56.1% vs. DEX 50.0%; 95% CI, −11.3%, 23.5%). PAL also demonstrated noninferiority to DEX (PAL 55.6% vs. DEX 50.0%; 95% CI, −12.0%, 23.2%). There were no statistically significant differences for all secondary endpoints between treatment arms.

Conclusion. This study showed that DEX-sparing regimens are noninferior to multiple-day DEX in terms of delayed TC rate in patients undergoing MEC. ClinicalTrials.gov *identifier.* NCT02135510. ***The Oncologist*** 2021;26:e173–e181

Implications for Practice: Chemotherapy-induced nausea and vomiting (CINV) in the delayed phase (24–120 hours after chemotherapy) remains one of the most troublesome adverse effects associated with cancer treatment. In particular, delayed nausea is often poorly controlled. The role of dexamethasone (DEX) in the prevention of delayed nausea after moderately emetogenic chemotherapy (MEC) is controversial. This study is the first to include nausea assessment as a part of the primary study outcome to better gauge the effectiveness of CINV control and patients' experience. Results show that a DEX-sparing strategy does not result in any significant loss of overall antiemetic control: DEX-sparing strategies incorporating palonosetron or multiple-day metoclopramide are safe and at least as effective as standard treatment with a 3-day DEX regimen with ondansetron in controlling delayed CINV—and nausea in particular—following MEC.

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) in the delayed phase (24–120 hours after chemotherapy) remains one of the most troublesome adverse effects associated with cancer treatment [1–4]. Clinical studies among patients receiving moderately emetogenic chemotherapy (MEC) demonstrate significantly higher incidences of delayed CINV compared with acute CINV (0–24 hours after chemotherapy), with twice as many patients requiring rescue antiemetic therapy during the delayed phase [5–7]. In particular, delayed nausea is often poorly controlled; patients experience nausea as more distressing than vomiting [8, 9]. Nausea is also frequently underreported by patients, leading to underestimation and undertreatment by clinicians [10, 11].

Many of the antiemetic agents currently available do little to relieve nausea [12]. Evidence-based antiemetic guidelines [13, 14] for patients receiving MEC recommend coadministration of a hydroxytryptamine-3 (5-HT_3) receptor antagonist (RA) and dexamethasone (DEX). DEX beyond 24 hours is recommended for agents with a known potential for delayed CINV such as oxaliplatin, monotherapy doxorubin, or cyclophosphamide. This recommendation is based upon results from studies performed in patients receiving regimens, which have recently been reclassified as highly emetogenic chemotherapy (HEC), such as anthracycline and cyclophosphamide (AC) combinations and carboplatin [15, 16]. Although prophylactic DEX has been generally considered safe, its administration may be associated with a wide range of side effects in the week after the initiation of chemotherapy [17]. Therefore, there is interest in minimizing dose and frequency of DEX in antiemetic regimens recommended for the prevention of acute and delayed CINV. A recent meta-analysis demonstrated that a DEX-sparing regimen consisting of single-dose DEX plus the second-generation 5-HT_3 RA palonosetron compared with 3-day DEX plus palonosetron did not cause any significant loss in protection against not only vomiting but also nausea during the delayed period [18]. However, only two of the eight studies included in this analysis involved MEC [19, 20]. The primary endpoint in both studies was complete response (CR; defined as no emetic episodes, no rescue medication) in the overall 5-day study period, whereas no nausea and no more than mild nausea in the delayed phase were single secondary endpoints or part of composite secondary endpoints, for which these trials were not powered. The results may therefore not accurately reflect the patients' actual experience of delayed nausea.

Another DEX-sparing option to improve CINV outcomes in MEC-treated patients is the addition of a third prophylactic drug to the antiemetic backbone containing a 5-HT_3 RA plus single-dose DEX. Receptors other than serotonergic, such as dopaminergic, histaminic, and muscarinic, may be the dominant receptors in the control of nausea [21–23]. Therefore, dopamine 2 (D_2)-receptor antagonists with prokinetic effects like metoclopramide, currently recommended only for the treatment of breakthrough emesis, could be useful in improving delayed nausea control. Comparative studies are lacking so far in MEC-treated patients investigating the efficacy of a three-drug prophylactic antiemetic regimen including a dopamine receptor antagonist with a 5-HT_3 RA plus single-dose DEX against delayed nausea. Herein we report the results of a randomized, phase III, noninferiority trial among patients receiving MEC, in which we studied the efficacy and safety of two DEX-sparing strategies consisting of single-dose DEX plus palonosetron, or a three-drug regimen with single-dose DEX plus the 5-HT_3 RA ondansetron and metoclopramide on days 2–3, both compared with standard 3-day DEX plus ondansetron. The objective was to demonstrate noninferiority of both DEX-sparing regimens to standard treatment in terms of control of delayed CINV with a focus on delayed nausea.

Materials, Methods, and Subjects

Study Design

This multicenter, open-label, randomized, phase III, noninferiority trial included patients at six enrolling sites in The Netherlands between June 2014 and June 2018. The institutional review board or ethics committee of each study site reviewed and approved the study protocol. All patients provided written informed consent according to international guidelines before treatment entry. The study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization guideline for Good Clinical Practice. This study was registered in ClinicalTrials.gov (number NCT02135510).

Patients

Eligible patients were aged ≥18 years, naïve to chemotherapy, able to speak and read the Dutch language fluently, and scheduled to receive the first course of MEC for treatment of a histologically or cytologically confirmed solid tumor malignancy. MEC agents could be administered intravenously as single agents or in combination with chemotherapy agents with low or minimal emetogenic potential. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0–1 and acceptable hematologic, hepatic, and renal functions. Patients were not eligible if they were scheduled to receive radiotherapy within 2 weeks before initiation of chemotherapy or between days 1 and 8 after the administration of chemotherapy. Additional exclusion criteria were: receipt of medication with antiemetic effect up to 48 hours before chemotherapy; vomiting, retching, or mild nausea up to 48 hours before chemotherapy; serious comorbidity conditions such as intestinal obstruction, active peptic ulcer, hypercalcemia, uncontrolled diabetes mellitus, pheochromocytoma, brain or leptomeningeal metastases, parkinsonism, epilepsy, or psychiatric disorders. Patients with a history of alcohol abuse or concurrent use of corticosteroids (similar to prednisone ≥10 mg), and pregnant or nursing women were also excluded.

Procedures and Outcomes

Eligible patients were randomly assigned (1:1:1 ratio) to receive study treatment. The method for concealment of allocation was by enclosing assignments in sequentially numbered, opaque, sealed envelopes provided by an independent third party (university medical center pharmacist). The envelopes were opened sequentially and only after the

envelope had been irreversibly assigned to the participant. Investigators who evaluated treatment response were not masked to group assignment. The allocated treatment was not masked to the respective patients and treatment physicians. However, treatment assignments were concealed from the institutions and patients until registration. In this study, three antiemetic regimens for prevention of delayed CINV were compared: ondansetron 8 mg i.v. and DEX 8 mg i.v. on day 1 with DEX 4 mg orally twice daily on days 2–3 (DEX arm); ondansetron 8 mg i.v. and DEX 8 mg i.v. on day 1 with metoclopramide 10 mg p.o. three times daily on days 2–3 (MCP arm); and palonosetron 0.25 mg i.v. and DEX 8 mg i.v. on day 1 with no additional doses of antiemetics (PAL arm). Dose, dosage, and route of administration of antiemetic treatment were according to current clinical guidelines (supplemental online Table 1). Ondansetron, metoclopramide, DEX, and benzodiazepines were permitted as rescue antiemetics during chemotherapy treatment.

During days 1–5 (0–120 hours), each patient completed a diary capturing emetic episodes, severity of nausea, and intake of rescue antiemetics. An emetic episode was defined as any episode of vomiting or retching, or combined vomiting and retching. Severity of nausea was evaluated using a 7-point Likert scale, ranging from no nausea (0 points) to nausea as bad it could be (7 points). On day 2, a telephone call was made by study personnel to ensure adherence to the required documentation and the prescribed study medication at home. On day 8, diaries were collected and reviewed. The proportions of patients with scores reflecting no vomiting, no nausea (score 0 on the Likert scale), no significant nausea (score ≤2 on the Likert scale), and no intake of rescue antiemetics were evaluated. The validated modified version of the Functional Living Index-Emesis (FLIE) questionnaire with a 5-day recall period was used to assess the impact of acute and delayed CINV on patients' daily lives [24]. The FLIE questionnaire (consisting of nine nausea-specific and nine vomiting-specific items) was completed by patients on days 2 and 6 after chemotherapy. Responses were marked on a 100 mm visual analogue scale (VAS) with anchors of 1 and 7. The proportion of patients with scores reflecting "no or minimal impact on daily life" (NIDL), defined as total FLIE score >108, was evaluated. The Dexamethasone Symptom Questionnaire (DSQ), a self-report questionnaire designed to be completed 1 week after the initiation of MEC, was used to rate the incidence and severity of DEX-associated side effects [17]. The DSQ includes eight items evaluating insomnia, gastroesophageal reflux, increased appetite, rash/acne, hiccups, oral candida, agitation, and feelings of depressing on ceasing medication. Responses were formatted using a four-point Likert scale (1 = not at all, 2 = a little bit, 3 = quite a bit, 4 = very much). The proportion of patients with moderate to severe side effects (score 3 or 4) was evaluated. The clinician-rated Abnormal Involuntary Movement Scale (AIMS) was used on day 8 to assess the severity of metoclopramide-associated dyskinesias [25]. The AIMS consists of four categories: facial and oral movements (four items), extremity movements (two items), trunk movements (one item), and global judgment (three items); each item was scored from 0 to 4 (i.e., none = 0 points, minimal = 1 point, mild = 2 points, moderate = 3 points, severe = 4 points). The proportion of patients with mild to severe dyskinesias (scores ≥2) was evaluated.

The primary efficacy endpoint was total control (TC; defined as no emetic episodes, no use of rescue medication, no nausea) in the delayed phase. Secondary efficacy endpoints included TC rates during the acute and overall (0–120 hours after chemotherapy) phases, no vomiting, no significant nausea, no nausea, no use of rescue antiemetics, CR (defined as no emetic episodes, no use of rescue medication), and complete protection (CP; defined as no emetic episodes, no use of rescue medication, no significant nausea) during all phases. Mean FLIE scores and FLIE scores reflecting NIDL during the acute/delayed phases were also evaluated as secondary endpoints. Safety was assessed by collection of side effects associated with DEX (evaluated with DSQ) and by collection of metoclopramide-associated dyskinesias (evaluated with AIMS).

Statistical Analysis

Assuming a delayed TC rate of 80% in the 3-day DEX arm and 60% in the 1-day DEX arms [19] with a noninferiority margin set at −20%, a total of 189 patients (63 patients per arm) were required under a two-sided 5% significance level and 80% power to show the noninferiority of the MCP and PAL arm to the DEX arm. Allowing a dropout rate of 20%, we aimed to enroll 237 patients (79 patients per arm). Number and proportion of patients with delayed TC were reported for each treatment group, and 95% confidence interval (CI) was estimated. If the lower limit of the 95% CI of the difference in delayed TC rates between the MCP and DEX arm or between the PAL and DEX arm was greater than the noninferiority margin of −20%, we would conclude that the MCP and PAL arms were noninferior to the DEX arm with regard to delayed TC. Because failure to control acute nausea and vomiting on the first day of chemotherapy will increase the risk of delayed nausea and vomiting [26], a bootstrap approach for analysis of covariance with a Bonferroni correction (Bonferroni post hoc test) was used to test the effect of antiemetic study medication on delayed TC, controlling for the effect of acute TC (covariate) on delayed TC rates. For secondary endpoints, statistical analyses used the same methods as for the primary endpoint. Baseline characteristics were compared between the treatment arms with the Mann-Whitney *U* test or chi-squared test. A value of $p \leq .05$ was considered statistically significant. All analyses were conducted by using IBM SPSS statistics version 22 (Chicago, IL).

Results

From June 2014 to June 2018, a total of 230 patients were randomly selected to receive antiemetic study treatment (Fig. 1). Baseline characteristics of all randomized patients are summarized in supplemental online Table 2. After randomization, 42 patients (n = 17 DEX arm, n = 13 MCP arm, n = 12 PAL arm) did not complete any study assessments and were therefore excluded from efficacy and safety analyses. Consequently, 189 patients (n = 60 DEX arm, n = 66 MCP arm, n = 63 PAL arm) represented the efficacy and

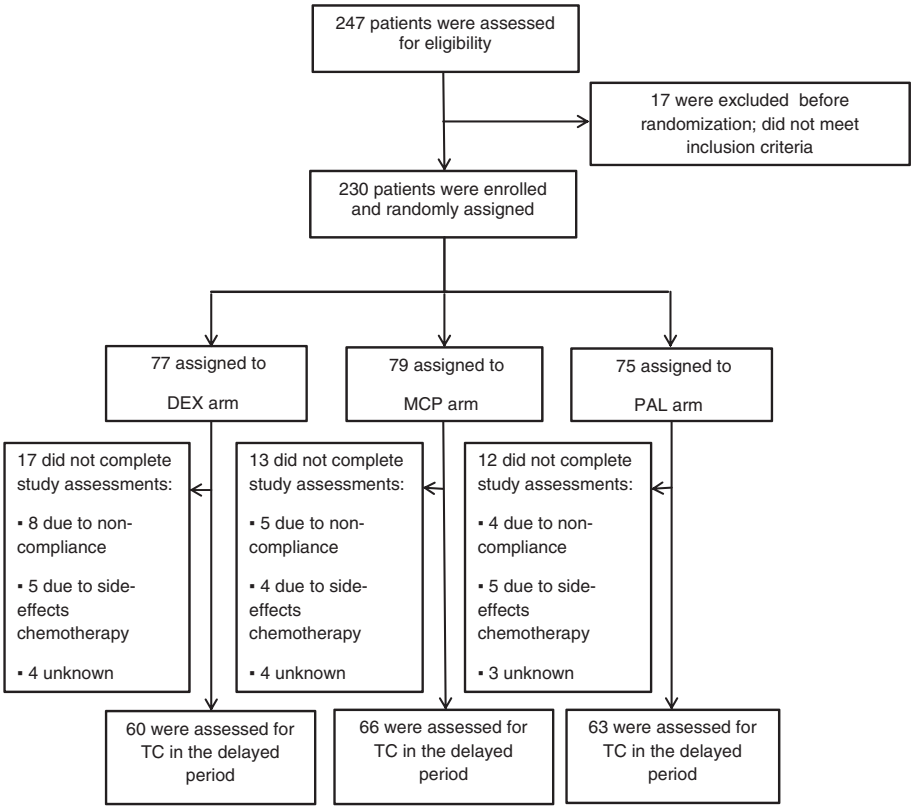

Figure 1. Trial profile.
Abbreviations: DEX, 3-day dexamathasone; MCP, 2-day metoclopramide; PAL, palonosetron; TC, total control.

safety population. Baseline characteristics of these patients were similar between treatment groups (Table 1). Slightly more patients were male (53.4%); colorectal cancer was the most common type of cancer (85.7%); oxaliplatin-based chemotherapy (81.5%) was the most commonly prescribed chemotherapeutic regimen.

Efficacy

Delayed TC rates were 50.0% (95% CI, 36.8–63.2) in the DEX arm, 56.1% (95% CI, 43.3%–68.3%) in the MCP arm, and 55.6% (95% CI, 42.5%–68.1%) in the PAL arm (Fig. 2). The 95% CI of the difference in delayed TC rates between the MCP and DEX arm was −11.3% to 23.5%; between the PAL and DEX arm −12.0% to 23.2%; both met the criteria for non-inferiority to the DEX arm. TC rates in the acute phase were 85.0% (95% CI, 73.4%–92.9%) in the DEX arm, 90.9% (95% CI, 81.3%–96.6%) in the MCP arm, and 79.4% (95% CI, 67.3%–88.5%) in the PAL arm. The 95% CI of the difference in acute TC rates was −5.6% to 17.0% between the MCP and DEX arm and −19.2% to 7.6% between the PAL and DEX arm. In the overall phase, TC rates were 46.7% (95% CI, 33.7%–60.0%) in the DEX arm, 54.0% (95% CI, 40.9%–66.6%) in the MCP arm, and 51.5% (95% CI, 38.9%–64.0%) in the PAL arm. The 95% CI of the difference in overall TC rates was −10.3% to 24.9% between the MCP and DEX arm and −12.7% to 22.3% between the PAL and DEX arm. After controlling for acute TC as covariate, we found no significant differences between the DEX arm and both the MCP (p = .68) and PAL arm (p = .35).

Response rates for all secondary efficacy endpoints during the acute phase favored the MCP arm, although differences were not statistically significant between treatment arms (Table 2). No vomiting, no significant nausea, and no nausea rates during the delayed phase were slightly higher in the DEX arm; no use of rescue medication and delayed CR rate were higher in the PAL arm; delayed CP rate favored the the MCP arm. All differences were not statistically significant between treatment arms. On day 2, mean ± SD FLIE score in the DEX arm was 118 ± 17.5, 117 ± 22.4 in the MCP arm, and 114 ± 21.7 in the PAL arm. Slightly more patients in the MCP arm reported NIDL (87.5%), compared with 86.0% in the DEX arm and 78.7% in the PAL arm (Fig. 3). Differences in NIDL scores on day 2 were not statistically significant between the MCP and DEX arms (p = .80) or between the PAL and DEX arms (p = .50). On day 6, mean FLIE score was 114 ± 16.1 in the DEX arm, 114 ± 21.5 in the MCP arm, and 114 ± 21.2 in the PAL arm. A higher proportion of patients in the PAL arm reported NIDL (80%), compared with 70.9% and 78.1% of the patients reporting NIDL in the DEX and PAL arm, respectively. Differences in NIDL scores were not statistically significant between between the MCP and DEX arms (p = .37), nor between the PAL and DEX arms (p = .21).

Safety

Table 3 shows the incidence of moderate to severe DEX-associated side effects (DSQ score 3–4). Increased appetite, rash/acne of the face, and indigestion/reflux were the most

Table 1. Patient baseline and disease characteristics (efficacy and safety population)

	All patients (*n* = 189), *n* (%)	DEX arm (*n* = 60), *n* (%)	MCP arm (*n* = 66), *n* (%)	PAL arm (*n* = 63), *n* (%)
Age, years				
Median (range)	65.0 (40–84)	64.0 (46–82)	65.0 (40–84)	67.0 (40–82)
≤55 years	30 (15.9)	9 (15.0)	14 (21.2)	7 (11.1)
>55 years	159 (84.1)	51 (85.0)	52 (78.8)	56 (88.9)
Gender				
Male	128 (55.7)	32 (53.3)	34 (51.5)	35 (55.6)
Female	102 (44.3)	28 (46.7)	32 (48.5)	28 (44.4)
Tumor type				
Colorectal	162 (85.7)	53 (88.3)	54 (81.8)	55 (87.3)
Ovarian	13 (6.9)	4 (6.6)	5 (7.6)	4 (6.3)
Lung	6 (3.2)	1 (1.7)	4 (6.1)	1 (1.6)
Gastric	4 (2.1)	1 (1.7)	2 (3.0)	1 (1.6)
Pancreatic	3 (1.6)	1 (1.7)	1 (1.5)	1 (1.6)
Other	1 (0.5)	0 (0.0)	0 (0.0)	1 (1.6)
Chemotherapy				
Oxaliplatin-based[a]	154 (81.5)	52 (86.7)	50 (75.8)	52 (82.5)
Carboplatin-based[b]	19 (10.0)	5 (8.3)	9 (13.6)	5 (7.9)
Irinotecan-based	11 (5.8)	2 (3.3)	5 (7.6)	4 (6.4)
Anthracycline-based[c]	4 (2.1)	1 (1.7)	2 (3.0)	1 (1.6)
Other	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.6)

[a]Oxaliplatin dose: 130 mg/m^2.
[b]Carboplatin dose: area under the curve (AUC) ≥4 mg/mL per minute (recently reclassified as highly emetogenic).
[c]Epirubicin dose: 50 mg/m^2.
Abbreviations: DEX, 3-day dexamethasone; MCP, 2-day metoclopramide; PAL, palonosetron.

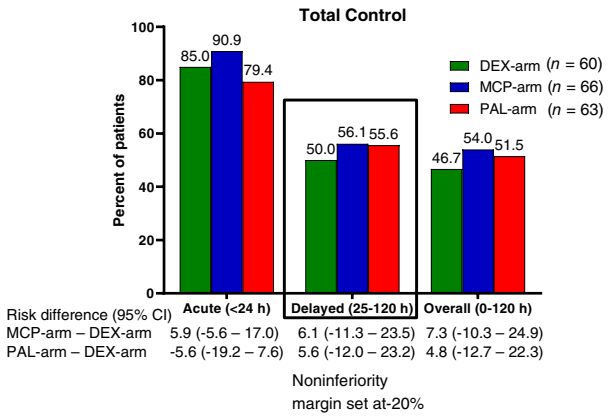

Figure 2. Total control rates. Noninferiority hypothesis in primary analysis was proven as the lower boundaries of the 95% CI of between-group difference were greater than the preset threshold (−20%).
Abbreviations: CI, confidence interval; DEX, 3-day dexamethasone; MCP, 2-day metoclopramide; PAL, palonosetron.

common side effects in all treatment arms. All side effects were easily manageable and controllable. Differences in incidence were not statistically significant between treatment arms. Metoclopramide-associated dyskinesias rarely occurred: six patients (9.1%) suffered from mild (AIMS grade 2) involuntary movements of the oral or facial musculature; four patients (6.1%) from mild involuntary movements of the upper or lower limbs. Severe involuntary movement of the facial musculature (AIMS grade 4) was reported by only one patient (1.5%). Severe involuntary movement of the jaw was also experienced by one patient. There were no DEX- or metoclopramide-associated side effects leading to withdrawal from the study.

Discussion

The present study demonstrates noninferiority of two DEX-sparing regimens consisting of single-dose DEX plus palonosetron, or a three-drug regimen with single-dose DEX plus ondansetron and 2-day metoclopramide to standard treatment with DEX beyond 24 hours in terms of delayed TC rate in patients undergoing MEC. There were no statistically significant differences for any of the secondary enpoints between treatment arms. Our findings suggest that both DEX-sparing regimens may be effective and safe alternatives to multiple-day DEX for control of delayed nausea and vomiting. This study is the first to include nausea assessment as a part of the primary study outcome to better gauge the effectiveness of CINV control and patients' experience.

Because of the subjective nature of nausea, its most reliable index is to measure no nausea rather than no significant nausea. The slightly higher TC rates in the MCP arm were reflected in a quality of life benefit, with a correspondingly higher proportion of patients with no impact on their functioning due to acute and delayed CINV. Although

Table 2. Secondary efficacy endpoints

Endpoint	DEX arm (*n* = 60), %	MCP arm (*n* = 66), %	PAL arm (*n* = 63), %	MCP-DEX risk difference (95% CI)	PAL-DEX risk difference (95% CI)
No vomiting					
Acute	95.0	97.0	88.9	2.0 (−4.9, 8.9)	−6.1 (−15.6, 3.4)
Delayed	88.3	77.3	77.8	−11 (−24.0, 2.0)	−10.5 (−23.6, 2.6)
Overall	83.3	75.8	74.6	−7.5 (−21.5, 6.5)	−8.7 (−23.0, 5.6)
No significant nausea					
Acute	90.0	93.9	85.7	3.9 (−5.6, 13.4)	−4.3 (15.8, 7.2)
Delayed	73.3	71.2	66.7	−2.1 (−17.7, 13.5)	−6.6 (−22.8, 9.6)
Overall	70.0	68.2	63.5	−1.8 (−18.0, 14.4)	−6.5 (−23.1, 10.1)
No nausea					
Acute	63.3	75.8	69.8	12.5 (−4.9, 29.9)	6.5 (−11.2, 24.2)
Delayed	48.3	43.9	50.8	−4.4 (−21.7, 12.9)	2.5 (−15.1, 20.1)
Overall	45.0	39.4	46.0	−5.6 (−22.9, 11.7)	1.0 (−16.6, 18.6)
No rescue use					
Acute	91.7	97.0	88.9	5.3 (−12.1, 22.7)	−2.8 (−20.8, 14.9)
Delayed	63.3	72.7	73.0	9.4 (6.9, 25.7)	9.7 (−6.7, 26.1)
Overall	60.0	69.7	71.4	9.7 (6.9, 26.3)	11.4 (−5.3, 28.1)
CR					
Acute	91.7	93.9	82.5	2.2 (−8.5, 12.9)	−9.2 (−21.1, 2.70)
Delayed	55.0	60.6	66.7	5.6 (−11.7, 22.9)	11.7 (−5,4, 28.8)
Overall	51.7	56.1	63.5	4.4 (−13.0, 21.8)	11.8 (−5.6, 29.2)
CP					
Acute	85.0	90.9	79.4	5.9 (−5.8, 17.3)	−5.6 (−17.9, 6.7)
Delayed	50.0	56.1	55.6	6.1 (−11.3, 23.5)	5.6 (−12.0, 23.2)
Overall	46.7	51.5	54.0	4.8 (−12.7, 22.3)	7.3 (−10.3, 24.9)

Abbreviations: CI, confidence interval; CP, complete protection; CR, complete response; DEX, 3-day dexamethasone; MCP, 2-day metoclopramide; PAL, palonosetron.

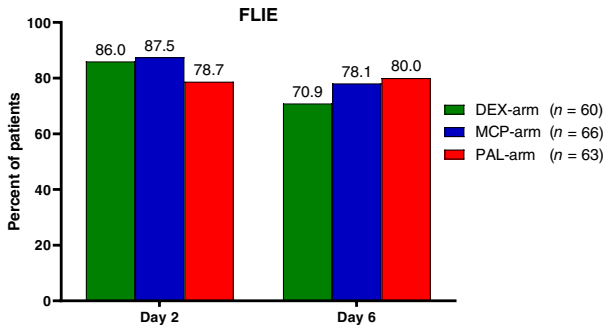

Figure 3. Percentage of patients with no or minimal impact on daily life (NIDL) based on the overall FLIE scores.
Abbreviations: DEX, 3-day dexamethasone; FLIE, Functional Living Index-Emesis; MCP, 2-day metoclopramide; PAL, palonosetron.

the differences were small and not statistically significant, it is encouraging that DEX-sparing strategies demonstrated some potential to improve quality of life.

Effective approaches to reduce patients' exposure to corticosteroids remain among the hot topics in clinical research on CINV. This is because the side effects of DEX may outweigh its benefits when used for CINV control. Patients receiving cumulative DEX doses may experience more severe side effects; recent prospective studies highlighted a potentially detrimental impact of short-term prophylactic dexamethasone in patients undergoing consecutive courses of emetogenic chemotherapy [27, 28]. The incidence of moderate to severe DEX-associated side effects in the present study was low compared with those reported in the study by Vardy et al. [17]. These differences may be explained by inaccuracy of the DSQ to determine which side effects were caused by DEX given after chemotherapy, by the i.v. DEX given before chemotherapy, by the chemotherapy itself (45% of patients in the study by Vardy et al. were treated with highly emetogenic AC combinations), or by other antiemetics or concomitant medications. Moreover, DEX-associated side effects in our study were only assessed after the first cycle of chemotherapy, whereas patients completed an average of four cycles in the study by Vardy et al.

The current study shows that a DEX-sparing strategy with ondansetron and metoclopramide on days 2–3 is a well-tolerated alternative prophylactic treatment to control CINV after MEC. Metoclopramide is a central D_2-receptor antagonist with activity at the chemoreceptor trigger zone and vomiting center, but it also acts on peripheral D_2, muscarinic, and 5-HT_4 receptors to induce prokinetic activity. At higher doses of metoclopramide (2 mg/kg), 5-HT_3 antagonist activity may also contribute to the antiemetic effect [29]. The daily dose of metoclopramide prescribed in this study (10 mg t.i.d. for 2 days) will not result in

Table 3. Dexamethasone-associated side effects

DSQ items	DEX arm (*n* = 60), *n* (%)	MCP arm (*n* = 66), *n* (%)	PAL arm (*n* = 63), *n* (%)
Indigestion/reflux	1 (1.7)	5 (7.6)	5 (7.9)
Insomnia	3 (5.0)	3 (4.5)	3 (4.8)
Increased appetite	10 (16.7)	8 (12.1)	9 (14.3)
Hiccups	2 (3.3)	0 (0.0)	0 (0.0)
Agitation	2 (3.3)	0 (0.0)	1 (1.6)
Depression	3 (5.0)	1 (1.5)	2 (3.2)
Rash/acne	4 (6.7)	7 (10.6)	3 (4.8)
Thrush/oral yeast infection	2 (3.3)	2 (3.0)	6 (9.5)

Only moderate to severe dexamethasone-associated side effects (DSQ score 3 or 4) are shown.
Abbreviations: DEX, 3-day dexamethasone; DSQ, Dexamethasone Symptom Questionnaire; MCP, 2-day metoclopramide; PAL, palonosetron.

5-HT_3 antagonist activity. High doses of metoclopramide (e.g., 200 mg every 4–6 hours) cause unacceptable extrapyramidal symptoms in more than 30% of patients [30]. Lower doses (25–50 mg) are associated with a very low incidence (<1%) of dyskinetic or extrapyramidal symptoms [31]. The U.S. Food and Drug Administration issued a black box warning for metoclopramide, given the high risk of developing tardive dyskinesia if metoclopramide use extends beyond 12 weeks [32]. However, this concern does not apply to the short-term course of metoclopramide in our study, in which only two patients suffered from grade 4 involuntary movements of the oral and facial musculature. These patients recovered without sequalae when metoclopramide was stopped.

This study also demonstrates that the control of delayed CINV—and nausea in particular—remains suboptimal with current prophylactic strategies in patients receiving MEC. Regardless of the use of DEX, TC in the delayed phase could not be achieved in almost 50% of patients. Only a minority of patients reported no nausea in the delayed and overall phase, and more than one third of all patients needed rescue antiemetics in the delayed or overall phase. New drugs and new combinations of drugs may improve control of CINV in patients who are treated with MEC. A recent meta-analysis demonstrated a clear clinically significant benefit with the addition of a neurokinin-1 (NK1) receptor antagonist in carboplatin-based chemotherapy, but not for MEC regimens [33]. The atypical antipsychotic olanzapine, which acts on many different receptors, particularly on the D_2, 5-HT_2c, and 5-HT_3 receptors, has been established as a highly effective antiemetic for patients undergoing HEC and AC combinations [34, 35]. Results of the Korean South West Oncology Group Study [36] showed that olanzapine in addition to palonosetron and dexamethasone did not significantly improve CR rates during the acute, delayed, and overall phase among previously untreated patients receiving MEC, although a clear benefit of olanzapine was observed in the management of vomiting and quality of life. Because data on the efficacy of olanzapine are limited, more studies are needed to evaluate the efficacy of olanzapine against delayed CINV, and delayed nausea in particular, in patients treated with MEC.

The present study has some limitations. First, 42 patients were eliminated from the full analysis set because these subjects did not complete study assessments, despite planned telephone calls on day 2 by research personnel to ensure adherence to the study protocol. Complement of study assessments was essential to perform the efficacy and safety analyses in this study. Failure to include these subjects in the full analysis set may have reduced statistical power and efficiency of the study. However, after taking observed data into account, there were no systematic differences between participants with complete data compared with those with missing data. Second, when this study was conducted, carboplatin was considered as a moderately emetogenic agent. Ultimately, 38 patients receiving carboplatin-based chemotherapy (evenly distributed across treatment groups) were included in the efficacy and safety analyses. Recently, carboplatin area under the curve (AUC) ≥4 mg/mL per minute has been reclassified as HEC [13, 14]. Consequently, these patients would no longer have been able to participate in this study but should have received a three-drug antiemetic regimen including a NK1 receptor antagonist according to updated antiemetic guidelines [13, 14]. Third, the modified FLIE questionnaire with a 5-day recall period was completed not only on day 6 after chemotherapy (in accordance with the validation study [24]) but also on day 2 after chemotherapy in order to obtain additional data on the impact of acute CINV on the patients' daily lives. It should be mentioned that the FLIE has not been validated for use on day 2, which may have affected the reliability of the questionnaire responses. Fourth, a large majority of patients were diagnosed with colorectal cancer (85.7%) and treated with oxaliplatin-based chemotherapy (81.5%). Therefore, the results of this study add information on the control of delayed CINV caused by oxaliplatin-based MEC in particular. It is difficult to generalize the results to other MEC regimens. A possible explanation for this overrepresentation of oxaliplatin is that only chemotherapy-naïve patients were eligible in the present study, and many MEC agents other than oxaliplatin (e.g., irinotecan, carboplatin AUC <4 mg/mL per minute, monotherapy doxorubicin or cyclophosphamide <1,500 mg/m^2) are rarely used as first-line chemotherapeutic agents. Fifth, the present study was designed to assess the control rates of delayed CINV after the first course of MEC. The noninferiority of DEX-sparing strategies after repeated MEC cycles should be determined in future studies. Finally, although baseline characteristics were similar between

treatment groups, we did not perform subgroup analyses categorized by individual patient factors that are well known to contribute to emetic risk, such as younger age, female sex, history of morning sickness, anxiety, and expectations of nausea or vomiting [37, 38].

Conclusion

Our study shows that a DEX-sparing strategy incorporating palonestron or multiple-day metoclopramide is safe and noninferior to DEX beyond 24 hours in terms of delayed TC rate in patients undergoing MEC, mainly consisting of oxaliplatin-based chemotherapy. Therefore, these regimens might be an alternative to standard treatment with multiple-day DEX.

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Disclosures

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