Double-blind, randomised, controlled study of the efficacy and tolerability of palonosetron plus dexamethasone for 1 day with or without dexamethasone on days 2 and 3 in the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy

M. Aapro1*, A. Fabi2, F. Nole3, M. Medici3, G. Steger4, C. Bachmann5, S. Roncoroni6 & F. Roila7

1Division of Oncology, Institut Multidisciplinaire d’Oncologie, Clinique de Genolier, Genolier, Switzerland; 2Department of Medical Oncology, Regina Elena National Cancer Institute, Roma; 3Department of Oncology, European Institute of Oncology, Milano, Italy; 4Department of Internal Medicine I, Division of Oncology, Medical University of Vienna, Wien, Austria; 5Department of Oncology, Medical University of Tubingen, Tubingen, Germany; 6Medical Division, Helsinn Healthcare SA, Lugano, Switzerland and 7Division of Medical Oncology, ‘S. Maria’ Hospital, Terni, Italy

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Background: To reduce side-effects of corticosteroid-containing antiemetic regimens, tailoring antiemetic schedules to specific requirements of different patients could be of benefit. We evaluated the possibility to reduce the total dose of corticosteroids when palonosetron, a long-acting second-generation 5-hydroxytryptamine-3 (5-HT3) receptor antagonist, is used.

Materials and methods: Double-blind, multicentre, noninferiority study of chemotherapy-naive breast cancer patients receiving 0.25 mg palonosetron and 8 mg dexamethasone on day 1, randomly assigned to receive placebo (n = 151) or 4 mg b.i.d. dexamethasone (n = 149) on days 2 and 3. Primary end point was complete response (CR) rate (no emesis, no rescue medication) in the overall (days 1–5) period. Secondary end points were CR rates in the acute (day 1) and delayed (days 2–5) periods, rates of no emesis and no nausea and impact on daily functioning (Functional Living Index-Emesis).

Results: Noninferiority between the two treatments was demonstrated by similar CR rates (P = 0.487) in the overall period. Most parameters showed that palonosetron and dexamethasone on day 1 only offer chemotherapy-induced nausea and vomiting protection similar to multiple-day dexamethasone administration.

Conclusion: In patients treated with a single injection of palonosetron on day 1, reducing dexamethasone is an option that is not associated with significant reduction in antiemetic control during the 5-day period or an impact on patient functioning.

Key words: CINV, dexamethasone, 5-HT3 receptor antagonist, nausea, palonosetron, vomiting

introduction

When uncontrolled, the effects of chemotherapy-induced nausea and vomiting (CINV) can be severely disabling for cancer patients. Despite prophylactic treatment, many patients continue to experience CINV after moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) [1, 2]. Palonosetron is a pharmaceutically unique second-generation 5-hydroxytryptamine-3 (5-HT3) receptor antagonist (RA) that shows high levels of protection from CINV during both the acute and delayed phases following a single i.v. 0.25 mg injection [1, 3]. Compared with the first-generation 5-HT3 RAs, the longer half-life and higher binding affinity of palonosetron may explain the observation that a single administration provides highly effective protection from CINV during both acute and delayed phases [3]. At present, a number of supportive care guidelines for prevention of CINV by National Comprehensive Cancer Network (NCCN) and Multinational Association for Supportive Care in Cancer (MASCC) consider palonosetron as either the preferred or recommended 5-HT3 RA for the control of CINV during HEC or MEC, respectively, not including anthracycline-containing regimens [4–6]. In phase 3 trials of patients receiving MEC, a single dose of 0.25 mg palonosetron offers extensive CINV protection over the 5-day observation period, covering both
acute and delayed emesis [1, 7]. In addition, palonosetron is associated with less significant nausea and less impact on patient functioning compared with the first-generation 5-HT3 RAs [8].

Corticosteroids such as dexamethasone are mentioned by guidelines as prophylaxis against low emetogenic chemotherapy when administered as monotherapy, although they are more commonly used to prevent either moderately or highly emetogenic CINV [9] due to their synergistic efficacy in combination with other antiemetics. Most studies have found that the addition of dexamethasone is superior to a 5-HT3 RA alone for control of emesis in both acute and delayed phases [8], consistent with current guidelines (MASCC, American Society of Clinical Oncology and NCCN) [4–7, 9]. In these guidelines, the scheduling and dosing of corticosteroids is tailored by taking into account the therapeutic setting and not the patient’s characteristics, which are of importance [9]. For example, the MASCC guidelines, recently updated in 2009, include a range of recommendations for the use of dexamethasone according to the risk of acute or delayed CINV in the MEC setting depending on the antiemetic drugs used.

Corticosteroids such as dexamethasone are generally considered safe when used in combination with other antiemetics [7, 9]. However, the clinician must consider that their administration may be associated with a range of side-effects, which may increase when administered as part of multiple-day antiemetic regimens [9, 10]. A recent survey investigating moderate to severe side-effects associated with dexamethasone administered for prophylaxis against delayed CINV after MEC included insomnia (45%), gastrointestinal symptoms (27%), agitation (25%), increased appetite (18%), weight gain (17%), skin rash (15%) and depression (7%) [11]. For these reasons, there is a particular interest in reducing their administration in certain clinical situations and/or in certain subsets of patients.

Accordingly, a double-blind study in chemotherapy-naive female breast cancer patients receiving MEC has been carried out. All patients received palonosetron plus dexamethasone on day 1 and were randomly assigned to receive either placebo or dexamethasone on days 2 and 3 to determine whether palonosetron might provide the opportunity to reduce the total corticosteroid dose with no loss of efficacy in delayed MEC.

**materials and methods**

**study population**

Chemotherapy-naive female patients with histologically or cytologically confirmed breast cancer, ≥18 years of age and scheduled to receive an MEC regimen (single dose of cyclophosphamide (<1500 mg/m²) and/or anthracycline (epirubicin, doxorubicin on day 1)) were eligible for inclusion. Additional inclusion criteria included Karnofsky performance status grade 60 or more life expectancy ≥3 months and acceptable hepatic and renal function [aspartate aminotransferase ≤2× upper limit of normal (ULN); creatinine level ≤1.5× ULN, respectively].

Exclusion criteria included known hypersensitivity to 5-HT3 RA or dexamethasone, scheduled to receive MEC (according to Hesketh classification level 3 or higher [12, 13]) on days 2–6 or HEC on days 1–6 or scheduled to receive radiotherapy on days 1–6; antiepileptic therapy (within 24 h of treatment initiation) or scheduled to receive (up to day 5) any drug with antiemetic effects, nausea or vomiting according to National Cancer Institute—common toxicity criteria of grade 2 or 3 in the 24 h before receiving study medication or pregnancy/breast-feeding. A signed informed consent was obtained from all patients before study entry.

**study design**

This prospective, double-blind, randomised, multicentre noninferiority study was conducted at 17 sites in Austria, Germany, Italy and Spain. At the first cycle of chemotherapy, patients were randomly assigned to receive either arm A or arm B, both receiving 0.25 mg palonosetron plus 8 mg i.v. dexamethasone on day 1, while on days 2 and 3, patients in arm A received placebo and patients in arm B received dexamethasone 4 mg p.o. b.i.d. On day 1, dexamethasone was administered 1 h before the infusion of chemotherapy and palonosetron as a bolus over 30 s, 30 min before the start of chemotherapy. On days 2 and 3, patients were given either oral dexamethasone or matching placebo, once in the morning and once in the evening.

**study objectives**

The primary objective was to show noninferiority between the two treatments from day 1–5 in terms of complete response (CR), as defined below. To demonstrate the noninferiority of the day 1 regimen, the lower boundary of the two-sided 95% confidence interval (CI) on the difference between the overall CRs for the two groups must be ≥15%.

**efficacy parameters**

Efficacy was monitored through clinical evaluations and a patient diary. From the start (time 0) until 120 h after the start of chemotherapy, the diary was used to document the date and time of emetic episodes and use of rescue medication, as well as daily nausea ratings [by visual analog scale (VAS); 0 mm ‘no nausea’ and 100 mm ‘as bad as it could be’]. Patients were allowed to take rescue therapy throughout the study for nausea or vomiting as needed. The choice of rescue antiemetic medication was at the discretion of the investigator, except for phenothiazines, which were prohibited due to their antiemetic properties. Clinical visits were carried out on days 1, 6 and between days 19 and 29.

All efficacy analyses started with administration of MEC (day 1, time 0) and continued through the following 120 h (day 5). The primary end point was CR rate (no emesis, no rescue medication) during the overall period (days 1–5, 0–120 h after chemotherapy). Secondary efficacy end points were CR rates in the acute (day 1, 0–24 h) and delayed (days 2–5, 24–120 h) periods and daily; complete control (CC) (no emesis, no rescue medication, with a maximum grade of mild nausea defined as a VAS <25 mm) in the overall, acute, delayed and daily periods; no emesis, no nausea (defined as VAS ≤5 mm), use or no use of rescue medication (percentage of patients) in the overall, acute and delayed periods. In addition, maximum severity of nausea (MSN) was evaluated in daily and overall phases. For cumulative assessments, only the maximum value of severity (i.e. the peak value) for each patient in each day was considered. Time to treatment failure (time to first emetic episode or time to first use of rescue medication, whichever occurred first) was evaluated during the 5 days following study drug administration.

Quality of life was measured using the Functional Living Index-Emesis (FLIE) questionnaire during the screening phase (referred to days 5–1) and on day 6 (referred to days 1–5); mean FLIE scores were totalled from nine questions in each of two domains (nausea and vomiting) for the overall phase, with each question scored by patients on a 7-point VAS scale with anchors corresponding to ‘none/not at all’ and ‘a great deal’ concerning the effect of CINV on daily functioning.

**safety**

Safety evaluation included assessment of all adverse events (AEs) and serious AEs, irrespective of their relationship with study drug for any study participant who received at least one dose of study medication (n = 151 for dexamethasone on day 1 and placebo on days 2 and 3, n = 149 for palonosetron + dexamethasone on days 1–3). Treatment-related adverse
events (TAEs) were classified according to their relationship with the study drug (i.e. possible, probable, definite or unassessable).

**Statistical analysis**

For primary efficacy analyses, CR rates during the overall phase (0–120 h) were compared between the two treatment groups. To demonstrate noninferiority of the P+D-d1 regimen, the lower boundary of the two-sided 95% CI on the difference between the overall CRs for the two groups (P+D-d1 regimen minus P+D-d1–3 regimen) had to be greater than –15%. The secondary parameters were interpreted in a descriptive manner: CR rates at all planned periods (except the overall phase primary end point) were analysed as for the primary end point, with the 95% CI of the difference between the treatment groups. In addition, for all time periods (including 0–120 h), a one-sided Cochran–Mantel–Haenszel (CMH) test stratified by centre was carried out. CC, percentage of patients with no emesis, with no nausea and without use of rescue medication were analysed using the one-sided CMH test stratified by centre. Time to treatment failure was assessed using Kaplan–Meier curves. Treatment groups were compared using a log-rank test. The severity of nausea, the FLIE scores and patient’s global satisfaction were evaluated with a one-sided Wilcoxon rank-sum test.

**Results**

A total of 300 chemotherapy-naïve female breast cancer patients receiving MEC were enrolled. The intent-to-treat population included 151 patients who received palonosetron + dexamethasone on day 1 and placebo on days 2 and 3 (P+D-d1) and 149 patients who received palonosetron + dexamethasone on day 1 and continued with dexamethasone b.i.d. on days 2 and 3 (P+D-d1–3). No clinically meaningful differences in demographic or baseline characteristics were noted between the two groups (Table 1).

**Complete response**

During the overall period, CR was found in 53.6% (95% CI 45.4% to 61.8%) of patients in the P+D-d1 arm and 53.7% (95% CI 45.3% to 61.9%) of patients in the P+D-d1–3 arm, with a between group difference of –0.0% (95% CI –1.17% to 11.6%). Noninferiority of the P+D-d1 regimen compared with the P+D-d1–3 regimen was demonstrated as the lower boundary of the two-sided 95% CI (–11.7%) was inferior to –15% (Figure 1). This result was confirmed by the Cochran–Mantel–Haenszel test (stratified by centre), which indicated the lack of statistically significant differences between groups.

Similar noninferiority of the P+D-d1 regimen was observed in the acute and delayed phases (Figure 1). In the acute phase, 69.5% of patients in the P+D-d1 arm achieved CR, compared with 68.5% in the P+D-d1–3 arm (P = 0.573). During the delayed phase, similar percentages of patients in the two arms achieved CR (Figure 1; P = 0.250).

Across both treatment groups and at all time intervals, the percentage of patients with CR was high (≥70%) (Figure 2).

**Control of emesis and nausea**

Across both treatment groups and at all time intervals, the percentage of patients with no emesis was high (≥70%) (Figure 2).
For the overall period, the percentage of patients with no emesis was similar between groups \((P = 0.429)\). In the acute phase, 80.1% and 79.2% \((P = 0.583)\) of patients reported no emesis, while in the delayed phase, 78.8% and 85.2% \((P = 0.077)\) of patients had no emetic episodes in the P+D-d1 and P+D-d1–3 groups, respectively. In the evaluation of daily occurrence of emetic episodes, no significant differences were observed between the two study groups, except on day 3 where patients receiving P+D-d1–3 experienced less emesis than patients receiving P+D-d1 (88.7% versus 96.6%, \(P = 0.004)\).

Figure 3 shows the percentage of patients with no nausea (VAS <5 mm) at all time intervals. Considering the overall period, the percentage of patients with no nausea in the two groups was similar \((P = 0.212)\). Likewise, there were no statistically significant differences with no nausea in the acute or delayed phases or at any other time intervals. For each daily and cumulative assessment, the median of the severity of nausea, with reference to the VAS scale (0–100 mm) was always <25 mm, i.e. no more than mild nausea in both treatment groups.

For each daily assessment in both groups, the mean as well as the median of the ‘MSN’ was always <25 mm, i.e. ‘no more than mild nausea’ (data not shown). For the acute phase, the mean MSN was similar in both treatment arms (19.6 and 23.7 for the P+D-d1 and P+D-d1–3 group, respectively; \(P = 0.643\)).

On days 2, 3 and 4, patients in the P+D-d1–3 group had lower MSN scores, but this difference reached statistical significance only on day 3 \((P = 0.028)\).

Regarding the probability of failure between both groups for all time intervals, the Kaplan–Meier estimate for the time to first emetic episode or first use of rescue medication was similar between groups. No statistically significant differences were observed \((P = 0.878)\).

Use of antiemetic drugs as rescue medication was low and similar across both groups. In the acute phase, 32 patients (21.2%) in the P+D-d1 group and 34 patients (22.8%) in the P+D-d1–3 group used rescue medication, while in the delayed phase, the number and percentage of patients using rescue medication remained low (31.8% and 28.9%, respectively). No statistically significant differences were observed at any time interval.

**quality of life**

For days 5–1, the mean FLIE scores for nausea were 59.1 and 59.5 for the P+D-d1 and P+D-d1–3 groups, respectively, confirming that no functional living impact of nausea was present before chemotherapy. For days 1 to 5 (overall period), the mean FLIE scores for nausea decreased from baseline, as expected, although they remained high and similar. No statistically significant differences between groups were observed (Figure 4; \(P = 0.140)\).

For days 5–1, the mean FLIE scores for vomiting confirmed that patients had no emesis before chemotherapy. For days 1–5, the mean FLIE scores for vomiting were similar. For the overall period, the difference between the two treatment groups was not statistically significant \((P = 0.640)\). For days 5–1, the mean combined nausea and vomiting FLIE scores were 19.4 and 120.0 for the P+D-d1 and P+D-d1–3 groups, respectively. For days 1–5, the mean FLIE scores for nausea and vomiting were similar for both treatment groups (105.1 and 105.8 for the P+D-d1 and P+D-d1–3 groups, respectively). No statistically significant differences were observed \((P = 0.245)\).

**safety**

In the safety population, the percentage of patients who experienced any AE was similar for both treatment groups, and

**Figure 2.** Percentage of patients with no emesis in the acute, delayed and overall intervals. \(P > 0.05\) one-sided Cochran–Mantel–Haenszel test (stratified by centre) indicate no difference between the two regimens.

**Figure 3.** Percentage of patients with no nausea during daily, delayed and overall intervals \(P > 0.05\) (Cochran–Mantel–Haenszel test stratified by centre) indicate no difference between the two regimens.

**Figure 4.** Quality of life evaluated with the functional living index-emesis (FLIE) questionnaire for nausea and vomiting. FLIE: nausea questions 1–9, emesis questions 10–18, score range 9–63, a higher score indicates less impact on patient functioning.
the percentage of patients reporting any treatment-emergent AEs was also similar across both treatment groups (Table 2). Among TAEs, a difference between the two groups was apparent for insomnia, a known and common AE associated with dexamethasone, which was higher in the P+D-d1–3 group (8.7%) than the P+D-d1 group (2.6%) (chi-square test, \( P = 0.023 \), post hoc analysis). The majority of TAEs were mild in severity and unrelated to the study medication. The most common TAEs in both groups were headache, constipation and erythema (Table 3).

Twelve patients in each group experienced clinically significant abnormal laboratory values. Slight, clinically significant shifts from baseline were observed in white blood cell counts, neutrophils and lymphocytes in both groups as expected from the chemotherapeutic regimens.

discussion

Novel anti-CINV regimens involving the use of antiemetic agents are currently being evaluated in certain patient subpopulations to understand whether different treatment approaches can offer additional protection against the debilitating impact of acute or delayed CINV or similar protection with a simplified antiemetic regimen. Guidelines recommend a 5-HT\(_3\) RA associated with concomitant administration of corticosteroids, and the use of dexamethasone in the delayed phase following HEC as well as MEC in certain circumstances. In some instances, however, dexamethasone may be contraindicated and patients often complain of side-effects associated with dexamethasone [11, 14]. This study indicates that when palonosetron is included in a regimen for control of CINV, comparable outcomes for overall emesis and nausea control can be achieved with dexamethasone given on 1 day only, without additional dexamethasone on days 2 and 3. In contrast with other studies that show a significant benefit of adding dexamethasone to first-generation 5-HT\(_3\) RAs for control during the delayed phase of CINV, the unique mechanism of action of palonosetron may explain the extended protection observed in the delayed phase, without the need for multiple-day dexamethasone. These data may therefore be of help to clinicians who desire to tailor therapy by reducing the overall exposure to dexamethasone, while still ensuring effective control of acute and delayed CINV and minimising the impact of chemotherapy on quality of life.

Overall, the additional parameters analysed in this study confirm the noninferiority outcome of the primary end point, both in terms of emesis and, interestingly, in control of nausea, even if 8% lower emesis control was observed on day 3 in patients receiving a single dose of dexamethasone on day 1, when compared with the group receiving dexamethasone for 3 days. In both groups, the trend for high emesis control was maintained with a clear increase of protection from day 1 to day 5. Emesis prevention in the whole delayed period was comparable with both dexamethasone regimens.

The percentage of patients with no nausea did not significantly differ between patients receiving the two treatment schedules in any of the evaluated time intervals ensuring similar daily or overall nausea control. Considering the grade of nausea, the MSN showed significant differences between the two study groups on day 3 in favour of multiple-day dexamethasone administration, although maximum nausea values during days 2–5 were always <25 mm value on the VAS, which is considered the threshold for mild nausea. Consequently, despite differences on the third day of treatment, effective overall control of nausea was achieved with palonosetron and dexamethasone administered on day 1 only. These trends are reflected in the time to treatment failure, a parameter measuring the time point of event occurrence, either an emetic episode or the need for rescue medication, which was not different between the two study groups.

In addition to clinical evaluations, the quality-of-life analysis supports the overall favourable clinical outcomes showing no differences on impact of daily life activities due to emesis or nausea despite the different dosing regimens; in fact, overall quality of life was preserved and did not differ between the two groups except on day 3.

These results are of particular interest as they were obtained in a population of patients that normally presents multiple risk factors for CINV such as receipt of multiple cycles of emetogenic chemotherapy, female gender and younger age. Although this study was not designed to evaluate the side-effect profiles of the two regimens, it was evident that patients receiving the multiple-day dexamethasone regimen experienced a significantly higher incidence of insomnia, a known treatment-related side-effect with dexamethasone.

There is little doubt that dexamethasone is a useful and effective addition to anti-CINV regimens and is recommended during the acute and delayed phases for patients undergoing HEC. However, recommendations for the use of dexamethasone in combination with other anti-CINV treatments for MEC vary, and in some cases, the benefits of dexamethasone need to be weighed against the increased risk of potential side-effects. The present study is therefore important as it provides evidence that in certain patients, tailoring

Table 2. Percentage of AEs and treatment-emergent AEs

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<th>P+D-d1 regimen</th>
<th>P+D-d1–3 regimen</th>
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<tr>
<td>Any AE</td>
<td>87.4% (132/151)</td>
<td>89.3% (133/149)</td>
</tr>
<tr>
<td>Treatment-emergent AE</td>
<td>25.2% (38/151)</td>
<td>28.9% (43/149)</td>
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<tr>
<td>Treatment-emergent SAE</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
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P+D-d1 regimen, patients who received palonosetron + dexamethasone on day 1 and placebo on days 2 and 3; P+D-d1–3 regimen, patients who received palonosetron + dexamethasone on day 1 and continued with dexamethasone b.i.d. on days 2 and 3.

AE, adverse event; SAE, serious adverse event.

Table 3. Treatment-related AEs

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<th>P+D-d1 regimen</th>
<th>P+D-d1–3 regimen</th>
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<tbody>
<tr>
<td>Headache</td>
<td>15.9% (24/151)</td>
<td>18.8% (28/149)</td>
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<tr>
<td>Constipation</td>
<td>2.6% (4/151)</td>
<td>7.4% (11/149)</td>
</tr>
<tr>
<td>Erythema</td>
<td>5.3% (8/151)</td>
<td>5.4% (8/149)</td>
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P+D-d1 regimen, patients who received palonosetron + dexamethasone on day 1 and placebo on days 2 and 3; P+D-d1–3 regimen, patients who received palonosetron + dexamethasone on day 1 and continued with dexamethasone b.i.d. on days 2 and 3.

AEs, adverse events.
Dexamethasone dosing to reduce exposure is not associated with a clinically significant reduction in antiemetic control during the 5-day observational period or impact on patient performance. For rare patients, the protection was insufficient on day 3, and therefore some might want to opt for a full dexamethasone regimen to avoid this risk, if they have no side-effects related to 3 days of dexamethasone. A recent single-arm study has also indicated that all antiemetics can be given on the same day in some circumstances [15].

In conclusion, the noninferiority design of this study demonstrates that the reduced dexamethasone dosing regimen offers high and similar protection as 3-day dosing, as demonstrated by the equivalent CR rates in the 5-day observation interval.

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**references**