Is a Dexamethasone-Sparing Strategy Capable of Preventing Acute and Delayed Emesis Caused by Combined Doxorubicin and Paclitaxel for Breast Cancer? Analysis of a Phase II Trial

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Key Words

Palonosetron · Dexamethasone · Chemotherapy-induced nausea and vomiting · Emesis · Doxorubicin · Paclitaxel · Breast cancer

Abstract

Objective: The effectiveness of palonosetron without delayed dexamethasone dosing against emesis was investigated in patients scheduled to receive the corticosteroid-containing combination of doxorubicin and paclitaxel (AT) for 3 cycles. **Methods:** Chemo-naïve women with breast cancer receiving doxorubicin (60 mg/m²) and paclitaxel (200 mg/m²) were eligible. Patients received palonosetron 0.25 mg intravenously before chemotherapy, however, all patients also received a premedication consisting of prednisone (25 mg orally the evening before therapy) and hydrocortisone (250 mg intravenously just before paclitaxel). The primary end point was complete control (CC; no vomiting, no rescue anti-emetics, and no more than mild nausea) during the overall phase (days 1–5) following cycle 1. **Results:** Seventy-six patients were enrolled and evaluable (median age 50 years). Fifty-six patients (74%; 95% CI 62–83%) achieved overall CC. Acute (day 1) and delayed (days 2–5) CC rates were 78 and 74%, respectively. No vomiting rates for the acute, delayed and overall phases were 85, 85

and 83%, respectively. An exploratory analysis showed only a small decrease in the probability of achieving CC between cycle 1 (74%) and cycle 3 (66%). **Conclusion:** The dexamethasone-sparing strategy prevented emesis in more than 70% of breast cancer patients receiving their initial cycle of AT chemotherapy.

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Introduction

Chemotherapy-induced nausea and vomiting (CINV) still remains among the most severe and concerning side effects of cancer treatment [1]. Acute CINV typically occurs within 24 h of chemotherapy, whereas delayed symptoms develop between days 2 and 5. A critical factor in guiding anti-emetic treatment is the ability of chemotherapy to induce a substantial risk of delayed emesis [1]. The combination of anthracycline and paclitaxel is traditionally classified as moderately emetogenic chemotherapy (MEC), and guidelines recommend a 5-HT₃ serotonin receptor antagonist (5-HT₃ RA) on day 1 plus dexamethasone on days 1 through 3 for the optimal prevention of acute and delayed CINV [2–4]. However, dexamethasone, taken for delayed emesis after MEC, has been reported to induce moderate-to-severe side effects

that may have a substantial impact on the patient's quality of life [5]. In addition, patients receiving paclitaxel receive high-dose dexamethasone (20 mg orally or intravenously administered at 12 and 6 h prior to chemotherapy) premedication to minimize the risk of severe hypersensitivity reactions. This premedication may result in side effects, including steroid withdrawal symptoms, hyperglycaemia, confusion and memory loss, insomnia, gastric discomfort, myopathy and depression [6, 7]. In addition, the incidence of these side effects may increase over time because patients undergo multiple cycles of paclitaxel. Although prednisone, a corticosteroid with a shorter half-life, may be more suitable than dexamethasone in the prophylaxis against major hypersensitivity reactions [8], there is a genuine need for tailoring the anti-emetic dosing of dexamethasone to reduce the overall exposure in patients who are scheduled to receive the corticosteroid-containing combination of anthracycline and paclitaxel.

Palonosetron is a second-generation 5-HT₃ RA with a greater binding affinity and a prolonged half-life compared to older agents [9]. Two early phase III trials in MEC indicated that single-dose palonosetron alone significantly increased CINV control compared with single-dose ondansetron or dolasetron during the delayed and overall phases [10, 11]. More recently, a phase III trial also showed superiority of palonosetron over granisetron, in combination with dexamethasone for 3 days, in the delayed phase in prevention of CINV caused by highly emetogenic chemotherapy (cisplatin or combined anthracycline and cyclophosphamide, AC) [12]. The 5-HT₃ RA palonosetron is the first and, at present, the only agent in the class to have a specific indication for the prevention of delayed nausea and vomiting associated with MEC regimens [9]. Two recent phase III trials also demonstrated that palonosetron plus single-dose dexamethasone administered either before a broad range of MEC or AC-containing regimens provide protection against overall CINV, which is non-inferior to palonosetron plus the conventional 3-day dexamethasone [13, 14].

A phase II trial was conducted to investigate the effectiveness of a dexamethasone-sparing regimen including palonosetron, without the need for dexamethasone dosing on days 2 and 3 after chemotherapy initiation, as prophylaxis for CINV in women with breast cancer receiving the corticosteroid-containing combination of doxorubicin and paclitaxel (AT). In this specific setting premedication including prednisone administered the evening before chemotherapy and hydrocortisone given just before

paclitaxel infusion replaced anti-emetic dexamethasone dosing on day 1. The longitudinal CINV assessments also provided an opportunity to explore anti-emetic outcome over consecutive chemotherapy cycles.

Patients and Methods

The institutional review board approved the study protocol, and written informed consent was obtained from all participants before enrolment. This mono-institutional, nonrandomized, phase II study was conducted in the framework of a single-arm study evaluating the feasibility of a sequential regimen including AT for 3 cycles followed by CMF for 3 cycles, all given as adjuvant or neoadjuvant therapy in women with high-risk operable breast cancer.

Patients and Treatment

Chemotherapy-naïve women were eligible if they presented with primary breast cancer and were aged 18 years or older. Patients who entered the main trial had histologically confirmed breast carcinoma that was either amenable to surgery (clinical stage T2 or T3, N0) or had undergone curative resection (pathological stage T1–3, N1–3). For the anti-emetic study, patients were considered ineligible if they experienced nausea or vomiting within 24 h prior to initiation of chemotherapy, were given drugs that could influence emesis other than drugs for chemotherapy premedication, or exhibited cognitive problems that would impair their ability to take part in the study.

Patients were given doxorubicin at a dose of 60 mg/m² by intravenous bolus followed by paclitaxel at 200 mg/m² infused over 3 h on day 1 of a 21-day cycle. Patients repeatedly received up to three cycles of this combination as a part of their planned treatment. Anti-emetic coverage consisted of a single intravenous dose of palonosetron (0.25 mg) given 30 min before the administration of doxorubicin on day 1 of each cycle. All patients also received a premedication consisting of prednisone (25 mg orally the evening before therapy), hydrocortisone (250 mg intravenously) plus chlorphenamine (10 mg intravenously or intramuscularly), and cimetidine (300 mg intravenously), all given 30 min before paclitaxel [8]. After chemotherapy, rescue medication for the treatment of nausea and vomiting was permitted on an as-needed basis. If patients satisfactorily completed the first cycle and its related study procedures, they could continue in the anti-emetic extension study for up to two additional chemotherapy cycles.

Study End Points

The primary efficacy end point of the study was the proportion of patients who achieved complete control (CC; defined as no vomiting, no rescue anti-emetics and no more than mild nausea) during the overall phase (days 1 through 5 after the first cycle of chemotherapy). Secondary end points were the proportion of patients who achieved the following during the overall, acute (0–24 h post-chemotherapy) and delayed phase (days 2 through 5 post-chemotherapy) in cycle 1: CC (not including overall phase), no vomiting and no nausea.

Before enrolment, the investigators of the anti-emetic study instructed eligible patients to complete a home record card for reporting any emetic episode, nausea or use of rescue anti-emetics

during the 5 days following each cycle. The severity of nausea was recorded by each patient on a graded scale (grade 0, defined as no nausea; grade 1 (referred to as mild), defined as loss of appetite; grade 2 (referred to as moderate), defined as reduced food/fluid intake; grade 3 (referred to as severe), defined as no fluid/food intake), according to the common terminology criteria for adverse events (CTCAE), version 3.0 [15]. Any serious adverse event judged by the investigator to be possibly, probably or definitely related to palonosetron was recorded and graded according to the CTCAE.

Statistical Methods

The study was planned according to Fleming's one-step study design [16]. We estimated that the dexamethasone-sparing regimen in women receiving AT would be considered ineffective if the proportion of patients achieving an overall CC was $\leq 45\%$ in cycle 1. The drug would be recommended for further study, with a 5% rejection error and a power of 80% if 39 or more of the total of 70 patients achieved CC. Assuming a 5% drop-out rate, 78 patients needed to be enrolled. However, study enrolment was prematurely closed after the first 76 patients were enrolled.

Primary and secondary end points were evaluated using an intention-to-treat analysis. In the primary analysis, efficacy data were reported as percentages with 95% confidence intervals (95% CI). To explore whether the anti-emetic control observed in cycle 1 would be sustained over consecutive cycles, a three-state model for cumulative transitional probabilities was used [17, 18]. This analysis of CC during an individual cycle evaluated the probability that patients would experience CC in a particular cycle, given their response so far. Patients could experience one of the following three possible outcomes: complete, major or failed control. For the primary end point of CC, the following definitions were used: conventional CC; major control (MC) – no vomiting and moderate nausea; and failure – at least one emetic episode and/or severe nausea. If a patient achieved CC or MC in a cycle and continued further in the study, the patient was then able to achieve CC, MC or failure in the following cycle. Patients who failed a cycle were considered to have failed all subsequent cycles. Efficacy data of patients who withdrew or discontinued for reasons other than anti-emetic failure or study drug toxicity were also not included in the probability computations for subsequent cycles. Therefore, the probability computations for each cycle were based on an assessable population consisting of those patients who achieved CC in the cycle being assessed, and who also achieved either CC or MC in all previous cycles. This approach allowed for fluctuations in a patient's level of response from one cycle to the next without actual treatment failure. The tolerability profile of interest in the present study was that of repeated dosing with palonosetron (i.e. over at least two cycles). All adverse event data over cycles 1–3 were recorded.

Results

A total of 76 women were consecutively enrolled into the study. Baseline characteristics for the study cohort are summarized in table 1. A substantial proportion of patients were younger than 50 years (41%), and approxi-

Table 1. Baseline characteristics for patients who entered cycle 1

	Patients (n = 76)	
	n	%
Gender		
Female	76	100
Age categories		
<50 years	31	40.8
≥ 50 years	45	59.2
Median (range)	50 (23–74)	
Alcohol consumption		
None	39	51.3
Every day ^a	37	48.7
Pregnancy emesis		
None	43	56.6
Yes	27	35.5
Unknown	6	7.9
Cancer diagnosis		
Breast	76	100
Tumour stage		
Early	76	100
Chemotherapy intent		
Neoadjuvant	9	11.8
Adjuvant	67	88.2
Doxorubicin dose		
60 mg/m ²	74	97.4
50 mg/m ²	2	2.6
Paclitaxel dose		
200 mg/m ²	74	97.4
175 mg/m ²	2	2.6

^a1–2 glasses of wine.

mately half of the patients (51%) had a history of no alcohol consumption. Thirty-six per cent of women had a history of pregnancy emesis. An elderly patient received a doxorubicin dose of 50 mg/m² and a paclitaxel dose of 175 mg/m² from cycle 1 onwards. An additional 2 older patients received a reduction in either the dose of doxorubicin (to 50 mg/m²) or paclitaxel (to 175 mg/m²) from cycle 1 onward. All changes were made at the discretion of the treating oncologist.

Primary and Secondary End Points in Cycle 1

All patients were fully evaluable for efficacy in cycle 1. The proportions of patients achieving CC during all time periods are shown in figure 1. The efficacy hypothesis in the primary analysis was sustained as 56 patients (73.7%; 95% CI, 62.3–83.1) achieved CC during the overall phase. For the acute and delayed phases, the majority of patients achieved CC (77.6 and 73.7%, respectively). Secondary efficacy analyses are presented in table 2. The proportion of vomiting-free patients was

Fig. 1. CC rates among the 76 patients who entered cycle 1. CC was defined as no vomiting, no rescue anti-emetics and no more than mild nausea. Vertical bars represent the upper limit of the 95% CIs.

high (>80%) within the acute, delayed or overall phases. For all time intervals, the proportion of nausea-free patients was greater than 50%.

Anti-Emetic Outcome over Consecutive Cycles

Of the 76 patients who entered cycle 1, 13 did not continue the study due to anti-emetic failure. A total of 63 patients completed a pre-study visit for cycle 2; of these, 3 did not receive palonosetron in cycle 2 due to a protocol deviation unrelated to the anti-emetic drug, while 1 patient was given a corticosteroid supplement for an allergic reaction to paclitaxel. None of these patients were included in the efficacy analysis for cycles 2 and 3. In cycle 3, 1 patient decided to continue chemotherapy at another hospital and 1 patient did not receive palonosetron due to protocol deviation unrelated to the anti-emetic drug. Neither of these patients were eligible for evaluation in the probability computations for cycle 3.

For overall CC, table 3 gives the cumulative transitional probabilities estimated for each cycle as well as the numbers of recorded response states per cycle. There was only a small decrease in the cumulative probability of a CC in the next cycle given the control of CINV between cycle 1 (74%) and cycle 3 (66%). Forty-one of the 45 patients (91%) with CC in cycle 3 experienced CC consistently throughout all cycles (i.e. none had an MC).

The subjective assessment by each patient of nausea severity in each treatment cycle is shown in table 4. The

Table 2. Secondary efficacy end points in cycle 1

Variable	n/N	%	95% CI
No vomiting			
Acute (day 1)	65/76	85.5	75.6–92.5
Delayed (days 2–5)	65/76	85.5	75.6–92.5
Overall (days 1–5)	63/76	82.9	72.5–90.6
No nausea			
Acute (day 1)	49/76	64.5	52.7–75.1
Delayed (days 2–5)	41/76	53.9	42.1–65.4
Overall (days 1–5)	41/76	53.9	42.1–65.4

n = Number of responders; N = number of patients.

Table 3. Estimated probabilities of CC and number of recorded response states in the overall phase (days 1–5) over consecutive cycles

	Cycle		
	1 (n = 76)	2 (n = 63)	3 (n = 51)
Estimated probability of CC ¹	0.74	0.70	0.66
CC	56	50	45
MC	7	1	3
Failure ²	13	8	1
Withdrawal ³	0	17	10
Evaluable patients	76	59	49

n = Number of entered patients at day 0.

¹ Cumulative probabilities estimated using a transitional probability analysis [15, 16].

² Failure defined as at least one emetic episode and/or severe nausea.

³ Includes failures from the previous cycle and patients no longer in the study.

Table 4. Severity of nausea in the overall phase (days 1–5) over consecutive cycles

Chemotherapy	Evaluable patients	Severity of nausea ¹ , n (%)		
		grade 1	grade 2	grade 3
Cycle 1	76	20 (26.3)	13 (17.1)	2 (2.6)
Cycle 2	59	24 (40.7)	4 (6.8)	0
Cycle 3	49	11 (22.5)	3 (6.1)	0

¹ Subjective assessment by each patient according to CTCAE v.3.0: grade 1 (mild), loss of appetite; grade 2 (moderate), reduced food/fluid intake; grade 3 (severe), no fluid/food intake.

majority of nausea was considered mild in severity during all treatment cycles; few patients reported moderate nausea on any study day during each treatment cycle (6.1–17.1% of patients). Only 2 patients experienced severe nausea during cycle 1.

Tolerability

Sixty-one patients who received at least two doses of palonosetron were evaluable for safety. Twenty-one patients (34.4%) in the safety cohort experienced at least one adverse event judged by the investigators to be possibly, probably or definitively related to palonosetron. The most common treatment-related adverse events were headache (21.3%) and constipation (13.1%). All adverse events were mild-to-moderate in severity, and no serious adverse events occurred during the study.

Discussion

The AT regimen is traditionally classified as an MEC, which is associated with an estimated acute emetic risk ranging from 30 to 90% [2–4]. However, optimal management of CINV includes scheduling anti-emetics throughout the full period of risk, which can continue for at least 2–3 days after the last dose of single-day MEC [1]. Therefore, recently updated international guidelines recommend palonosetron plus dexamethasone on day 1, with dexamethasone also given on days 2 and 3, to optimally prevent CINV caused by MEC [2, 3]. The phase II study described here yielded two key findings: (1) single-dose palonosetron without delayed dexamethasone dosing resulted in a high rate of CC against acute and delayed CINV caused by the corticosteroid-containing combination of AT in a homogeneous cohort of chemotherapy-naïve women with breast cancer, and (2) there was only a small decrease in the probability of achieving CC over consecutive cycles.

Although the standard end point of complete response (i.e. no vomiting and no rescue anti-emetics) represents the most comprehensive indicator of anti-emetic efficacy, CC was the primary end point for this trial in order to account for the incidence of both nausea and vomiting in the assessment of efficacy. Since 74% of the patients achieved CC (i.e. no vomiting, no rescue anti-emetics and no more than mild nausea) in the overall phase of cycle 1, the dexamethasone-sparing strategy was successful in the prevention of CINV for the majority of patients receiving the moderately emetogenic combination of AT. It should

be noted that a complete protection against nausea occurred in 54% of the patients during the overall phase of cycle 1, but the symptoms were considered mild in severity by the majority (57%) of patients experiencing nausea. A similar pattern for nausea severity was also observed in cycles 2 and 3.

The study findings are of interest because the adequate control of nausea remains an unmet need in patients receiving emetogenic chemotherapy [19]. Therefore, a more clinically appropriate assessment of anti-emetic efficacy should rely on not only the improvement in control of vomiting but also nausea, which can strongly affect quality of life [20]. In a phase III trial assessing whether a 5-HT₃ RA was more effective than prochlorperazine for control of delayed nausea caused by doxorubicin-containing chemotherapy, 671 chemo-naïve patients (90% women with breast cancer) were given a short-acting 5-HT₃ RA plus dexamethasone (12 mg orally or 10 mg intravenously) before chemotherapy initiation on day 1, followed by one of three regimens for days 2 and 3: (1) any 5-HT₃ RA (except palonosetron) taken as standard dose intravenously or orally; (2) prochlorperazine orally three times a day, and (3) prochlorperazine taken as needed [21]. The study showed that older 5-HT₃ RAs are no better than prochlorperazine in prevention of delayed nausea caused by doxorubicin-containing chemotherapy, but the number of patients receiving the highly emetogenic combination of AC was not available for this trial. In spite of the intrinsic limitations of inter-study comparisons, it is interesting to point out that the proportion of vomiting-free patients in the dexamethasone-sparing group was consistent with that seen among patients receiving either 5-HT₃ RA or prochlorperazine on days 2 and 3 in both the acute (85 vs. 82%, respectively) and delayed (85 vs. 71%, respectively) phases. Likewise, the proportion of nausea-free patients in the dexamethasone-sparing group compared well with that seen among patients receiving either 5-HT₃ RA or prochlorperazine on days 2 and 3 in both the acute (64 vs. 48%, respectively) and delayed (54 vs. 23%, respectively) phases. In addition, these findings are of interest as they were obtained in a cohort that included a substantial proportion of women younger than 50 years (41%) as well as patients with a history of no alcohol consumption (51%) or pregnancy emesis (35%), all of which are known risk factors for CINV [1]. A recent retrospective analysis also showed that younger age is a major risk factor for chemotherapy-induced nausea, and that breast cancer patients experience more nausea than patients suffering from other cancers [22].

Recently, two phase III trials evaluated dexamethasone dosing, comparing 1- and 3-day dexamethasone dosing combined with palonosetron in patients receiving either a broad range of MEC or AC-containing regimens [13, 14]. Findings from these trials suggest that tailoring dexamethasone dosing in patients treated with palonosetron is not associated with a clinically significant loss in anti-emetic control. It is also interesting to note that, in clinical practice, many patients tend to neglect taking delayed anti-emetics, and a low rate of adherence by outpatients to delayed dexamethasone has recently been reported among breast cancer patients receiving anthracycline-based chemotherapy [23, 24]. Therefore, further clinical investigations are needed to define optimal schedules for use of dexamethasone against CINV.

In an exploratory analysis using the three-state model for transitional probabilities [17, 18], single-dose palonosetron without delayed dexamethasone dosing provided sustained control over consecutive cycles in terms of overall CC, with estimated protection rates that did not vary by more than 8 percentage points across all three cycles. Since a strong correlation appears to exist between failure in the delayed phase of a cycle and poor outcome in the acute phase of the next cycle [25], the small decrease observed in overall CC rate from cycle 1 to cycle 3 supports the belief that palonosetron, with its known efficacy against delayed CINV, contributed to the maintenance of benefit throughout consecutive cycles [9].

A limitation of our study is that patients assessed the severity of nausea by the CTCAE rather than a more conventional tool using either a categorical rating scale or visual analogue scale. We acknowledge that a more standardized assessment might ensure better comparisons

with findings from other studies. However, it is well known that the optimal control of nausea still remains an unmet need in CINV research [19].

Conclusion

The distinct pharmacology of the second-generation 5-HT₃ RA palonosetron provides a rationale behind the efficacy of dexamethasone-sparing strategy in prevention of delayed CINV caused by MEC [9]. In this phase II study, single-dose palonosetron without delayed dexamethasone dosing achieved a high rate of overall control against CINV in a high-risk cohort of breast cancer patients undergoing the corticosteroid-containing combination of AT. An exploratory analysis suggested that there was only a small decrease in the probability of achieving CC over multiple cycles. In view of the present results and the literature data [13, 14], the dexamethasone-sparing strategy is a reasonable therapeutic option for the prevention of CINV in women receiving the first cycle of AT. For subsequent cycles, we suggest that delayed dexamethasone doses could be offered to patients achieving poor initial control of delayed symptoms.

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