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ORIGINAL ARTICLE

The feasibility of dexamethasone omission in weekly paclitaxel treatment for breast cancer patients

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Abstract

Objectives Patients with breast cancer who receive weekly paclitaxel therapy may experience deleterious effects associated with prophylactic dexamethasone use for 12 consecutive weeks. Approximately 90% of paclitaxel hypersensitivity reactions (HSRs) occur within the first 10 to 15 min of the first two infusions. We investigated the feasibility of dexamethasone withdrawal between weeks 3 and 12 (W3 and W12) in early stage breast cancer patients treated with weekly paclitaxel at the standard dose (80 mg/m^2).

Methods All patients received intravenous prophylaxis of dexamethasone 20 mg, ranitidine 50 mg, and diphenhydramine 50 mg in the first 2 weeks (W1 and W2) of treatment. Provided that no serious (G3/G4) HSRs events occurred, dexamethasone was omitted between W3 and W12, while ranitidine and diphenhydramine were continued. The primary end point was the incidence of any grade HSRs during the treatment period, and the secondary end points were quality of life and weight changes.

Results Twenty-five patients were included in the study, and 300 infusion cycles of paclitaxel were evaluated for HSRs. The overall incidence of HSRs was 0.6% (2 events), and both of these events occurred in the first week. There were no incidents of serious HSRs or anaphylaxis and no G3 or G4 toxicities. Scores from the EORTC QLQ-C30 questionnaire did not change significantly for the global health status/quality of life scale or for the symptoms scales, although changes in scores differed significantly for the functional scales. There were no clinically relevant weight changes during the treatment period.

Conclusions Dexamethasone withdrawal from W3 to W12 in early stage breast cancer patients treated with weekly paclitaxel is feasible. The incidence of all grades of HSRs was comparable to that reported in trials with dexamethasone for 12 consecutive weeks, and no serious events (G3/G4) occurred. Studies with larger sample sizes are needed to confirm our results which are important, especially for patients for whom corticosteroids are contraindicated.

Keywords Paclitaxel · Hypersensitivity reactions · Prophylaxis · Dexamethasone

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Introduction

Paclitaxel is an antimicrotubule agent used as monotherapy or combined with other antineoplastic drugs for treatment of many solid tumors. Due to its hydrophobic properties, it must be emulsified in a vehicle containing Cremophor-EL (polyethoxylated castor oil and ethanol), which can lead to hypersensitivity reactions (HSRs) [1].

The clinical spectrum of paclitaxel HSRs is characterized by flushing, pruritus, urticaria, hypotension, erythematous rash, tachycardia, low back pain, chest pain, and respiratory distress. Approximately 90% of these events occur within the first 10 to 15 min of the first two infusions and are thought to be due to an IgE-mediated release of histamine [1–4]. Factors such as infusion time and the use of prophylactic drugs (corticosteroids and H1/H2 receptor antagonists) can reduce the incidence of such events. With prophylactic measures, the incidence of serious reactions such as dyspnea requiring a bronchodilator, symptomatic hypotension requiring intervention, angioedema, and generalized urticaria is approximately 2 to 4% [1, 2]. The management of mild to moderate (G1/G2) reactions includes infusion interruption, administration of symptomatic agents as clinically indicated, and prolongation of infusion time. If there is complete remission of symptoms, paclitaxel rechallenge can be considered. If serious (G3/G4) adverse events occur, rechallenge is not indicated regardless of symptom resolution.

The recommended paclitaxel infusion time is 3 h for doses of 135 to 225 mg/m^2, but at doses of up to 90 mg/m^2, administration over the course of 1 h is considered safe [5–7]. Prophylactic medication is recommended in all cycles with doses greater than 135 mg/m^2, as follows: (1) 20 mg oral dexamethasone (or equivalent), 12 and 6 h prior to infusion, (2) 50 mg of diphenhydramine (or equivalent) intravenously 30 to 60 min prior to infusion, and (3) cimetidine (300 mg) or ranitidine (50 mg) intravenously 30 to 60 min prior to infusion. [1] There are no guidelines regarding the schedule for prophylactic use of dexamethasone for weekly infusions [8]. One commonly used regimen is 10 mg IV weekly when the paclitaxel dosage is less than 90 mg/m^2 [5].

In breast cancer patients receiving weekly adjuvant or neoadjuvant paclitaxel treatment, dexamethasone use for 12 consecutive weeks may lead to several deleterious effects such as hyperglycemia, insomnia, gastritis, fluid retention, weight gain, immune suppression, acne, skin changes, cognitive impairment, and adrenal suppression [5, 8]. In studies of modified dexamethasone dosage schedules (reduction, tapering, or dose omission) that sought to minimize the adverse side effects of weekly exposure, increased incidence of serious HSRs was not reported [9–14].

The purpose of this study was to evaluate the outcomes of dexamethasone omission (overall incidence of any grades of HSRs, serious toxicities, weight changes and quality of life) between W3 and W12 of adjuvant or neoadjuvant paclitaxel treatment in patients with breast cancer.

Materials and methods

The clinical trial was approved by the Institution's Ethics Committee. Eligibility criteria for enrollment in the study included breast cancer patients in whom neoadjuvant or adjuvant weekly paclitaxel treatment at the standard dose (80 mg/m^2) was indicated, ability to make an informed consent prior to enrollment, histological confirmation of breast cancer, age ≥ 18 years, ECOG ≥ 2, adequate organ function, and controlled comorbidities. Exclusion criteria were chronic use of corticosteroids for any reason, prior use of taxanes in any context, combination of paclitaxel with any other antineoplastics, such as platinum, antiangiogenics, or trastuzumab, personal history of hypersensitivity to any components of the paclitaxel vehicle, and metastatic disease.

All patients received the paclitaxel infusion over the course of 1 h. The HSR prophylaxis regimen was administered intravenously 30 min prior to paclitaxel infusion. Dexamethasone 20 mg IV, ranitidine 50 mg IV, and diphenhydramine 50 mg IV were administered during W1 and W2. Provided that no serious HSRs occurred, dexamethasone was discontinued and prophylaxis between W3 to W12 included only ranitidine 50 mg IV and diphenhydramine 50 mg IV. All patients received Ondansetron 8 mg IV before all cycles of chemotherapy.

Prophylactic or therapeutic corticosteroids for chemotherapy-induced nausea and vomiting were allowed.

The primary end point was the incidence of any grade HSRs during the overall treatment period and secondary end points were weight changes and quality of life. We defined HSR as any adverse reaction that could be attributed to paclitaxel infusion that occurred within the infusion period.

The required number of infusions to detect a difference of 5% in HSRs beyond the expected value of 4% was 190 (power = 90% and alpha error = 0.05, one-sided test). Assuming that each patient would receive ten infusions of weekly paclitaxel without dexamethasone between W3 and W12, 19 patients would be required. Taking into account possible drop-outs, a sample size of 25 patients was chosen to meet the pre-specified power level.

Medical visits with clinical evaluations and toxicity assessment were performed at the following times: pre-enrollment, pre-W3, pre-W6, pre-W9, and post-W12. The assessment of HSR characteristics and grading was performed at each clinical visit and recorded as reported by the patient. HSRs were described and graded according the Common Term Criteria for Adverse Events (CTCAE) version 4.03 of the National Cancer Institute (NCI) [15]. Anaphylaxis was considered a separate event but was also assessed. The patients were

weighed at each clinical visit and completed the EORTC-QLQ C30 quality of life (QoL) questionnaire at the pre-W3 and post-W12 visits [16, 17].

Results

A total of 27 patients were enrolled in the study from August 2016 to January 2017 at the Brazilian Institute of Cancer Control. Two patients were excluded: one for personal history of ranitidine allergy and the other for metastatic disease progression during the treatment. Sociodemographic of the patients and clinical characteristics of their cases are presented in Table 1. The mean age was 49.5 years (range 25–71 years).

Table 1 Sociodemographic and clinical characteristics of the 25 patients

	Number	Percentage (%)
Age in years, median (range)		49.5 (25–71)
Sex		
Female	25	100
Male	0	0
ECOG		
0	23	92
1	2	8
Staging		4
I	1	1
II	8	32
III	16	64
Immuno-histochemistry profile		4
Luminal A	1	4
Luminal B	17	68
Triple negative	7	28
Chemotherapy context	14	56
Neoadjuvant	14	56
Adjuvant	11	44
Comorbidities		
0	15	60
1	7	28
2	2	8
3 or >	1	4
Planned anthracycline cycles completed		
Yes	24	96
No	1	4
Taxane first (pre-anthracycline)		4
Yes	1	1
No	24	96
Prophylactic corticosteroid with A		
Yes	25	100
Yes	25	100
No	0	0

The majority of the patients had an ECOG performance status of 0 (92%), were assessed to be in clinical or pathological stage III (64%), had a luminal B immunohistochemical profile (68%), and were in neoadjuvant treatment (56%). Only 1 patient had received a taxane-first regimen (pre-anthracycline), and 96% of patients completed the anthracycline when it was initially administered. All patients received prophylactic dexamethasone for chemotherapy-induced nausea and vomiting in the anthracycline phase.

A total of 300 cycles of weekly paclitaxel treatment distributed among the 25 enrolled patients were evaluated: 50 dexamethasone-on cycles (W1 and W2) and 250 dexamethasone-off cycles (W3 to W12). All HSR events occurred in the dexamethasone-on period (W1), as follows: one G2 event (facial flushing that promptly resolved after infusion interruption and administration of 200 mg of intravenous hydrocortisone) and one G1 event (self-limited mild palpitations). In the dexamethasone-off periods, there were no HSRs of any grades. The most common chemotherapy-related toxicities were assessed at all clinical visits, as follows: fatigue, nausea, vomiting, constipation, diarrhea, myalgia, neuropathy, and mucositis. There were no G3 or G4 toxicities during the treatment period.

Although prophylactic or therapeutic corticosteroids for chemotherapy-induced nausea and vomiting were allowed during the taxane chemotherapy cycles, no corticosteroids were needed for this purpose.

No significant changes in weight were observed in any of the weeks of treatment in which weight was measured (Fig. 1).

In assessing quality of life, the global health status/quality of life score and the symptoms scales from the EORTC-QLQ C-30 questionnaire did not result in statistically significant differences between the weeks when dexamethasone was administered and the weeks that it was not. Only the functional scale scores differed significantly ($p = 0.02$) between the prophylaxis treatment schedules. Table 2 shows the mean and the standard deviation for the quality of life analysis from the EORTC-QLQ C-30 scale by dexamethasone on and off periods.

Discussion

Deleterious effects of prolonged dexamethasone exposure during weekly paclitaxel treatment are well characterized, and many modified prophylaxis strategies have been evaluated, including reduction, tapering, and omission of dexamethasone. Green et al. reported no increase in serious HSRs events with a tapering dexamethasone schedule (from 10 to 4 mg), with an overall incidence of allergic reactions of 2.3%. [9]

Berger et al. demonstrated that it is safe to omit dexamethasone, diphenhydramine, and famotidine in patients who do

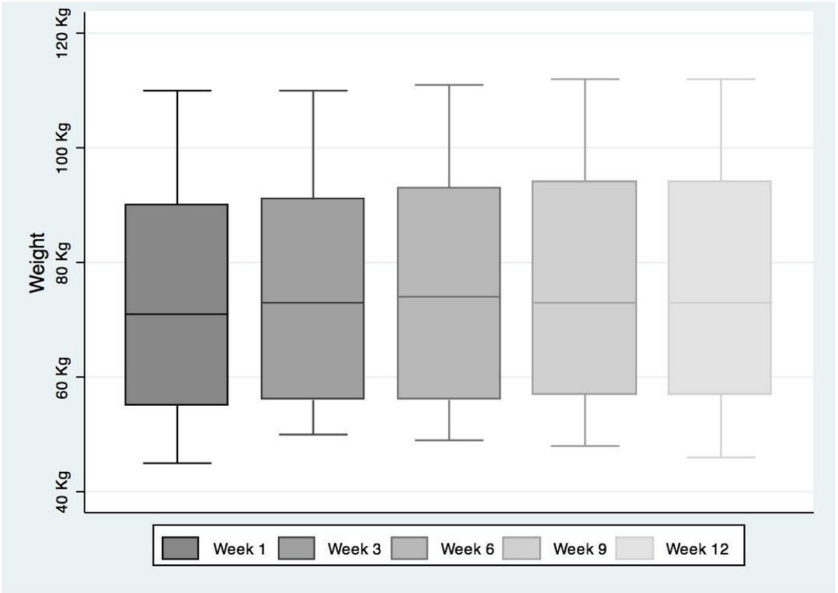

Fig. 1 Weight variation by week of treatment

not develop any grade HSRs in the first two cycles of weekly paclitaxel treatment, with a 4% incidence of HSRs (all grades) and less than 1% of serious adverse events in the first 2 weeks [14]. Quock et al. reported in a retrospective analysis that the incidence of three weekly paclitaxel (135–225 mg/m2) HSRs was 4% among 348 patients (comprising 1608 infusions), and 100% of those occurred within the first infusion. Based on these findings, a premedication protocol was instituted prospectively in 30 patients who were receiving weekly paclitaxel treatment (doses up to 90 mg/m^2), and none of them exhibited an HSR [11].

Similarly, we found that 100% of HSRs occurred in the first week of exposure and that no patient developed an HSR at a later infusion, even when dexamethasone was omitted. The incidence of HSRs in our study was 4%, which is concordant with previous reports [11, 14].

Several trials have shown that, for several reasons, patients exhibit an increase in body mass index (BMI) after adjuvant and/or neoadjuvant chemotherapy, mainly with the adriamycin plus cyclophosphamide (AC)-paclitaxel protocol. Prolonged corticosteroid exposure during this regimen may be an important factor. Ricci et al. reported a change in median pre- and post-chemotherapy BMI from 27.4 to 28.3 ($p < 0.001$) for those patients who received AC-paclitaxel. In our trial, however, there was not a significant change in body weight over the course of treatment [18]. Despite the small sample size (only 25 patients), this result suggests that the omission of dexamethasone after week 2 could minimize weight gain in this population.

Quality of life assessment is another important endpoint in clinical trials, as it provides information regarding the emotional, social, and physical well-being of the patient [19, 20]. For this reason, we decided to include a QoL questionnaire in our study. Based on previous studies in similar populations, we expected a worsening of the QLQ-C30 scores as a result of the chemotherapy. Our results showed that neither global health status/quality of life scores nor the symptoms scales changed significantly during treatment and only the functional scale was affected. In such a small sample size, it is not possible to identify the factors responsible for these findings, but dexamethasone omission could be one of them.

Table 2 Comparison of EORTC QLQ C30 questionnaire scales in dexamethasone on and off periods

	Mean (SD)	CI (95%)	*P* value
Global Health Scale (pre-week 3)	78.57 (± 17.02)	(71.55–85.60)	$p = 0.11$*
Global Health Scale (post-week 12)	72.28 (± 16.93)	(65.29–79.27)	
Functional Scale (pre-week 3)	81.42 (± 15.41)	(75.06–87.78)	$p = 0.02$**
Functional Scale (post-week 12)	72.51 (± 20.22)	(64.16–80.86)	
Symptoms Scale (pre-week 3)	22.61 (± 19.89)	(14.39–30.82)	$p = 0.46$**
Symptoms Scale (post-week 12)	24.99 (± 18.91)	(17.19–32.80)	

*T test

**Wilcoxon signed-rank test

Conclusion

Dexamethasone withdrawal from W3 to W12 in breast cancer patients who received neoadjuvant or adjuvant weekly paclitaxel is both feasible and safe. The incidence of HSRs was similar to that reported in trials with dexamethasone for 12 consecutive weeks, and no serious HSRs (G3/G4) occurred. Studies with larger sample sizes are needed to confirm our results which are important, especially for patients for whom corticosteroids are contraindicated.

Compliance with ethical standards

The clinical trial was approved by the Institution's Ethics Committee.

Conflict of interest The authors declare that they have no conflict of interest.

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