Feasibility of stopping paclitaxel premedication after two doses in patients not experiencing a previous infusion hypersensitivity reaction

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Abstract

Purpose Paclitaxel-based chemotherapy continues to be an integral component in the treatment of many solid tumors. Prolonged use of paclitaxel may result in repeated doses of premedications and potential unwanted side effects. Infusion hypersensitivity reactions occurring beyond the second dose are infrequent and not well characterized. We hypothesized that patients whose paclitaxel premedications were discontinued after two doses were unlikely to experience infusion hypersensitivity reactions with subsequent paclitaxel doses.

Methods Patients receiving paclitaxel-based chemotherapy who did not experience an infusion hypersensitivity reaction with their first or second dose had their paclitaxel premedications discontinued. The primary endpoint was to estimate the incidence of rescue medication for the treatment of paclitaxel infusion hypersensitivity during doses 3 to 6 for patients whose paclitaxel premedications had been discontinued.

Results After receiving the first two doses of paclitaxel-based chemotherapy without experiencing an infusion hypersensitivity reaction (any grade), 55 breast cancer patients had their premedications discontinued for all remaining paclitaxel doses. None of these patients required rescue medication to treat an infusion hypersensitivity reaction with subsequent doses.

Conclusions In patients who have not experienced an infusion hypersensitivity reaction with the first two doses of paclitaxel, discontinuation of paclitaxel premedications may be considered an option without an increased risk of infusion hypersensitivity requiring rescue medication.

Keywords Abbreviated · Paclitaxel · Premedication · Prophylaxis · Hypersensitivity

Introduction

Paclitaxel is commonly used in the treatment of a variety of solid tumors. More recently, the use of weekly paclitaxel has demonstrated superior efficacy and tolerability in the treatment of early stage and metastatic breast cancer [1, 2]. Due to its hydrophobic properties, paclitaxel must be emulsified in a vehicle consisting of 50% polyoxyethylated castor oil (Cremophor EL) and 50% ethanol. Despite premedication
with a corticosteroid and both histamine-1 and histamine-2 receptor antagonists. Hypersensitivity reactions (all grades) during intravenous administration of paclitaxel (135 to 300 mg/m² as a 3- or 24-h infusion) for the treatment of solid tumors in clinical studies occurred in 41% of patients, and “severe” (grade 3 or higher) hypersensitivity reactions occurred in 2% of patients [3]. Recent literature using paclitaxel for the treatment of breast cancer at doses between 80 and 90 mg/m² given as a 1-h infusion report a similar incidence (less than 3%) of grade 3 or higher hypersensitivity reactions [1, 4].

Previous studies have demonstrated that a simplified, intravenous premedication regimen consisting of dexamethasone and both histamine-1 and histamine-2 receptor antagonists administered 30 min prior to paclitaxel infusion can successfully reduce the incidence and severity of these reactions with comparable clinical efficacy to older regimens that employed dexamethasone 20 mg given orally 12 and 6 h and immediately prior to paclitaxel, although some remain critical of this simplified approach [5–7]. The most frequently used corticosteroid in the prevention of paclitaxel-induced hypersensitivity reactions is dexamethasone, which is among the most potent and longest acting of the corticosteroids. With prolonged use of paclitaxel, especially when given in a once weekly fashion, patients are exposed to repeated doses of dexamethasone. Side effects associated with short-term and prolonged use of corticosteroids are well documented, including hyperglycemia, insomnia, gastritis, fluid retention, weight gain, immune suppression, acne, skin changes, osteoporosis, mental status changes, and adrenal suppression. In addition, when administered as an intravenous bolus, dexamethasone has been associated with perianal pruritis. Diphenhydramine, the most commonly employed histamine-1 receptor antagonist for the prevention of paclitaxel-induced hypersensitivity, is commonly associated with drowsiness and can paradoxically cause dystonia and restlessness when 50 mg is administered intravenously [8].

To minimize the adverse effects of corticosteroids, several strategies exploring an alternative paclitaxel premedication regimen have been published including incorporation of a paclitaxel test dose, dexamethasone dose reduction, or use of a dexamethasone tapering schedule [9–12]. In an attempt to further simplify paclitaxel premedication and avoid unnecessary side effects caused by premedication regimens, we hypothesized that discontinuing paclitaxel premedications after the first two doses of paclitaxel would not result in an increased usage of rescue medications to treat infusion hypersensitivity reactions for subsequent paclitaxel doses. This is in contrast to standard paclitaxel premedication regimens in which patients may continue to receive premedications prior to each dose of paclitaxel, even if they had not experienced a previous infusion hypersensitivity reaction. To test this hypothesis, a clinical trial was designed.

Materials and methods

Patients Eligibility criteria included patients ≥18 years old able to give informed consent and scheduled to receive at least four doses of paclitaxel as a single agent or in combination with trastuzumab, bevacizumab, gemcitabine, or other drug combination (excluding cisplatin or carboplatin) for the treatment of any stage breast cancer; patients receiving concurrent radiation; patients currently enrolled in another clinical trial provided that the other trial did not prohibit the discontinuation of paclitaxel premedications; and patients receiving intermittent oral steroids for nausea or for acute inflammatory conditions (i.e., methylprednisolone Dosepak) and inhaled, intranasal, or topical corticosteroids were also eligible. Exclusion criteria included patients receiving therapeutic daily doses of systemic corticosteroids; patients receiving paclitaxel albumin bound; history of grade 3 hypersensitivity reaction to Cremophor EL-containing medications (paclitaxel, cyclosporine, ixabepilone, teniposide), docetaxel or paclitaxel albumin bound; patients who had received at least one dose of paclitaxel, docetaxel, or paclitaxel albumin bound within the last 12 months; patients receiving paclitaxel in combination with carboplatin or cisplatin (due to risk of hypersensitivity with platinum compounds); and patients who were pregnant. The research protocol was approved by the cancer institutional review board. All patients provided written informed consent prior to receiving their first dose of paclitaxel-based chemotherapy.

Treatment Enrolled patients beginning paclitaxel-based chemotherapy received standard paclitaxel premedications (dexamethasone 20 mg IVP, diphenhydramine 50 mg IVP, and famotidine 20 mg IVP) all given at least 30 min prior to the start of paclitaxel. If a patient was receiving paclitaxel in combination with other chemotherapy, the paclitaxel was infused first. For paclitaxel doses less than 100 mg/m², the drug was added to a DEHP-free infusion container of 0.9% NaCl or 5% dextrose water 250 mL and infused over 60 min. For paclitaxel doses more than 100 mg/m², the drug was added to a DEHP-free infusion container of 0.9% NaCl or 5% dextrose water 500 mL and infused over 180 min. If patients did not experience an infusion hypersensitivity reaction (any grade) with either of the first two paclitaxel (doses), dexamethasone, diphenhydramine, and famotidine were discontinued prior to the third dose and for all subsequent paclitaxel doses. Patients who experienced an infusion hypersensitivity reaction (any grade) with the first or second dose of paclitaxel (regardless if rescue medication was administered) were not eligible to have their premedication regimen discontinued. Patients receiving subsequent doses of paclitaxel after premedications were discontinued who experienced an infusion hypersensitivity reaction were...
to have paclitaxel premedications reinstituted and managed at the discretion of the prescribing physician.

Endpoints and assessment The primary endpoint was to estimate the incidence of rescue medication usage during paclitaxel doses 3 through 6 for patients whose premedication regimen was discontinued. Previous studies have not adequately defined what constitutes a “severe” or “clinically relevant” infusion reaction, what scale/scoring system was used to grade them, and how many patients actually received parenteral rescue medications to treat these reactions. We selected the use of rescue medication as our primary endpoint, rather than occurrence of an infusion hypersensitivity reaction, because the former is a more measurable endpoint given the difficulty of grading these reactions.

Clinical signs and symptoms of paclitaxel hypersensitivity reactions (Table 1) may vary. Grading of these hypersensitivity reactions is challenging due to the fact that no standard criteria have been developed: NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 3.1 for “Allergic Reaction/Hypersensitivity” (Table 2) was not all encompassing; for example, paclitaxel infusion hypersensitivity may also include diaphoresis, anxiety, tachycardia, symptomatic chest pain, and back pain. Furthermore, in routine clinical practice, parenteral “rescue” medications are often administered at the onset of the infusion hypersensitivity reaction to minimize the severity and progression of the reaction. Therefore, the use of parenteral medications in symptomatic patients is not restricted to CTCAE grade 3 (and higher) reactions only.

During paclitaxel infusions, patients experiencing any of the symptoms listed (Table 1) were considered to have experienced an infusion hypersensitivity reaction. The use of rescue medication for the treatment of paclitaxel infusion hypersensitivity was defined as the administration of at least one parenteral rescue medication (excluding 0.9% sodium chloride) including hydrocortisone, diphenhydramine, or epinephrine. Each patient’s electronic chemotherapy order contained standing orders enabling the chemotherapy nurse to identify and treat a hypersensitivity reaction as follows: stop the infusion, call an additional nurse into the room, notify the physician, and administer hydrocortisone 50 mg IVP and diphenhydramine 50 mg IVP. If at any time the patient exhibits severe signs of angioedema or bronchospasm, administer epinephrine 0.3 mg IM, call the physician to discuss further management of the reaction including fluids, oxygen, and reinitiation of the infusion if the reaction resolves. Patients were monitored for an infusion hypersensitivity reaction and rescue medication usage and had data recorded for up to six doses of paclitaxel, after which time the patient’s data collection for the trial was completed as the incidence of infusion hypersensitivity reactions beyond this point would be increasingly rare. Paclitaxel lot numbers and manufacturer information were recorded by the pharmacy staff. The chemotherapy nurses were not blinded; they knew what dose number of paclitaxel the patient was receiving and whether or not the patient was receiving premedication. The chemotherapy nurse remained in the patient room during the first 10 min of the paclitaxel infusion for the first three doses to closely monitor for any grade hypersensitivity reaction. The patient had a call button to alert the nurse for problems occurring when the nurse was not present.

Statistical analysis This observational study was designed to enroll 70 subjects to estimate the incidence of rescue medication required for paclitaxel doses 3 through 6. Assuming 20% of patients would not be eligible for our primary analysis due to various reasons (including hypersensitivity with the first two doses), 54 subjects would be needed to estimate the incidence. Although the incidence is thought to be low, the true incidence of rescue medication usage after the second dose is unknown; a 0% to 5% incidence of rescue medication during doses 3 to 6 was considered acceptable. If 3 of the 54 subjects who had paclitaxel premedications discontinued would require rescue medication during doses 3 to 6, the incidence would be 5.6% with a 95% confidence interval of 1.2% to 15.4%. No inferential testing was done to compare this incidence rate to historical controls as these rates are not known. Consequently no formal power analysis was used to estimate the sample size. If any patients required rescue medication after the discontinuation of paclitaxel premedications, an exact logistic regression analysis would determine if any of the demographics were associated with the incidence of rescue medication. The trial was to be stopped if there were 8 or more subjects out of the first 15 in the protocol population that required rescue medication. The trial would continue to full accrual if 7 or less required rescue medication out of the first 15. The probability of stopping the trial early was <0.001 if the true rescue medication incidence during cycles 3 to 6 was 5%. If the true incidence was 15% or 25%, then the probability of stopping early was 0.001 or 0.017, respectively.

The protocol population, defined as those patients who did not experience an infusion hypersensitivity reaction (any grade) with their first two paclitaxel doses and who received their remaining doses of paclitaxel with no premedications, was used in the primary analysis of estimating the incidence of rescue medication in doses 3 through 6. Patients receiving subsequent doses of paclitaxel after premedications were

| Table 1 | Symptoms of hypersensitivity reactions |
|---------|------------------------------------------|
| Flushing | Hypertension                              |
| Urticaria| Hypertension                              |
| Rash | Hypertension                              |
| Diaphoresis | Tachycardia                         |
|         | Chest pain | Anxiety                           |
|         | Back pain  | Abdominal pain                     |
| Adverse event | Short name | Grade | 1 | 2 | 3 | 4 | 5 |
|---------------|------------|-------|---|---|---|---|---|
| Allergy reaction/hypersensitivity (including drug fever) | Allergy reaction | Transient flushing or rash; drug fever <38°C (<100.4°F) | Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F) | Symptomatic bronchospasm, with or without urticaria; parental medication(s) indicated; allergy-related edema/angioedema; hypotension | Anaphylaxis | Death |
| Remark: urticaria with manifestations of allergic or hypersensitivity reaction graded as allergic reaction/hypersensitivity (including drug fever) | Also consider: cytokine syndrome/acute infusion reaction |
| Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip) | Rhinitis | Mild, intervention not indicated | Moderate, intervention indicated | – | – | – |
| Remark: rhinitis associated with obstruction or stenosis is graded as obstruction/stenosis of airways—select in the pulmonary/upper respiratory category | Autoimmune reaction | Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated | Evidence of autoimmune reaction involving a nonessential organ or function (e.g., hypothyroidism) | Reversible autoimmune reaction involving function or a major organ or other adverse event (e.g., transient colitis or anemia) | Autoimmune reaction with life-threatening consequences | Death |
| Also consider: colitis; hemoglobin; hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); thyroid function, low (hypothyroidism) | Serum sickness | Serum sickness | – | – | Present | – | Death |
| Navigation note: splenic function is graded in blood/bone marrow category | Navigation note: urticaria as an isolated symptom is graded as urticaria (hives, welts, wheals) in the dermatology/skin category | vasculitis | Mild intervention not indicated | Symptomatic, nonsteroidal medical intervention indicated | Steroid indicated | Ischemic changes; amputation indicated | Death |
| Allergy/immunology—other (specify) | Allergy—other (specify) | Mild | Moderate | Severe | Life threatening; disabling | Death |
Results

Baseline characteristics of all 70 enrolled patients are summarized in Table 3. Patients were enrolled at two outpatient chemotherapy infusion centers between August 2009 and March 2010. The type of chemotherapy regimen received is reflected in Table 4. Fifteen (21%) patients were not included in the primary analysis for the following reasons: consent withdrawn after the first dose (n=1); paclitaxel stopped prior to third dose due to paclitaxel toxicity; pneumonitis and myelosupression accompanied with refusal to receive blood products (n=2); hypersensitivity reaction experienced with the first dose of paclitaxel and therefore continued standard paclitaxel premedication in future cycles (two of these patients were rechallenged with paclitaxel the same day and successfully completed their entire course of therapy, while another patient was not rechallenged but rather changed to paclitaxel albumin bound given the severity of the infusion hypersensitivity reaction; n=3); paclitaxel premedications continued for other reasons despite not having hypersensitivity with the first or second dose; itching unrelated to infusion, delayed dermatologic toxicity, and patient preference (n=3); and paclitaxel premedications discontinued after the second dose but requested premedications be resumed with later doses in hopes of alleviating noninfusion-related toxicities—plantar skin peeling, lower extremity rash and facial burning, rash on dorsal arm, itching, indigestion, and allergic rhinitis (n=6).

Fifty-five patients who had paclitaxel premedications discontinued were included in the primary analysis; none of these patients required parenteral rescue medication with subsequent paclitaxel doses, and no infusion hypersensitivity reactions (any grade) were observed. Of these 55 patients, 47 (85%) were receiving 80–90 mg/m² of paclitaxel and 8 (15%) were receiving 175 mg/m². These 55 patients received all scheduled doses of paclitaxel (314 doses, of which 204 were administered without paclitaxel premedication). The incidence of parenteral rescue medication in our study was 0.0% with an exact one-sided binomial 95% confidence interval of 0.0–5.3%.

Discussion

Paclitaxel infusion hypersensitivity reactions are well characterized; regardless of paclitaxel dose or infusion rate, up to 95% of hypersensitivity reactions occur during the first or second dose, and in almost all cases the hypersensitivity reaction develops within the first 5–10 min of the infusion [13, 14]. The overwhelming majority of patients who experience an initial hypersensitivity reaction can successfully resume and complete paclitaxel treatment [9]. In a pooled toxicity analysis of over 800 patients receiving paclitaxel as a single agent for the treatment of solid tumors, no grade 3 or higher discontinuation. who experienced an infusion hypersensitivity reaction requiring rescue medication were to have standard premedications resumed for later paclitaxel doses and managed at the discretion of the prescribing physician; these patients were also included in the primary analysis. Patients who experienced an infusion hypersensitivity reaction (any grade) with the first or second dose of paclitaxel (regardless if rescue medications were administered) were not eligible to have premedications discontinued and were not included in the primary analysis.

Table 3 Baseline patient characteristics

| Characteristic                                    | n (%)       | Age in years, median (range) | 51 (31–78) |
|--------------------------------------------------|-------------|------------------------------|------------|
| Female sex, n (%)                                | 69 (99)     | Male sex, n (%)              | 1 (1)      |
| Tumor type                                       |             | Breast, n (%)                | 70 (100)   |
| Clinical breast cancer stage                     |             | Neoadjuvant, n (%)           | 14 (20)    |
| Previous lifetime exposure to paclitaxel,        |             | Stage I, n (%)               | 7 (10)     |
|         docetaxel or paclitaxel albumin, n (%)     |             | Stage II, n (%)              | 30 (43)    |
| Chronic medical conditionsa                      |             | Stage III, n (%)             | 14 (20)    |
| Yes, n (%)                                       | 47 (67)     | No, n (%)                    | 23 (33)    |

a One or more of the following: coronary artery disease, hypertension, diabetes, depression, bipolar disorder, generalized anxiety disorder, hyperthyroid, hypothyroid, asthma, COPD, GERD, hyperlipidemia, osteoarthritis, rheumatoid arthritis, lupus, irritable bowel syndrome, fibromyalgia, migraine, cerebral palsy, colorectal cancer

Table 4 Chemotherapy regimens

| Regimen Description                         | n (%)       |
|---------------------------------------------|-------------|
| Paclitaxel 80 mg/m² IV every 7 days×12 doses | 31 (44)     |
| Paclitaxel 80 mg/m² IV every 7 days×12 doses + trastuzumab 4 mg/kg loading dose followed by 2 mg/kg IV every 7 days | 19 (27)     |
| Paclitaxel 175 mg/m² IV every 14 days×4 doses | 10 (14)     |
| Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days indefinitely + bevacizumab 10 mg/kg every 14 days | 6 (9)       |
| Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days×4 cycles + bevacizumab/placebo 10 mg/kg every 14 days | 4 (6)       |
paclitaxel infusion hypersensitivity reactions occurred beyond the third dose [3]. Other investigators observed two patients (5%) who experienced a “clinically relevant” initial hypersensitivity infusion reaction occurring beyond the second dose [13]. Paclitaxel hypersensitivity reactions have been attributed to the vehicle or the drug itself [12, 14]. Interestingly, paclitaxel albumin bound (Abraxane™) which does not contain Cremophor EL can be safely administered without premedications and there were no grade 3 or higher hypersensitivity reactions reported in a randomized comparative trial with paclitaxel albumin bound given every 3 weeks [15].

Paclitaxel monotherapy or combination therapies with trastuzumab represent important options for the treatment of early stage and metastatic breast cancer. Recent in vitro reports suggest dexamethasone may inhibit paclitaxel cytotoxicity or may interfere with trastuzumab-induced cell growth inhibition [16, 17]. Together these findings support the use of nonsteroid-containing premedication regimens.

In the current study, the incidence of infusion hypersensitivity reaction (all grades) with the first or second dose of paclitaxel was observed to be 4% (n=3), and the incidence of serious infusion hypersensitivity reactions (grade 3 or 4) to be less than 1% (n=1), which is consistent with previous reports [1, 3, 4]. We were unable to compare the results of our primary endpoint (0 patients requiring rescue medication after premedications were discontinued) to historical controls since the true incidence of rescue medication usage after the second dose has not been characterized in the literature.

Interestingly, in our trial, a subset of nine (13%) patients who despite having no infusion hypersensitivity reactions felt that the late side effects attributed to paclitaxel (such as plantar skin peeling, lower extremity rash and facial burning, rash on dorsal arm, itching, indigestion, and allergic rhinitis) could be ameliorated by premedications and requested that they be continued (n=3) or resumed after stopping (n=6). Following discontinuation of dexamethasone, no patients requested an antiemetic premedication be added for nausea.

There are several limitations to this trial including a small sample size and lack of a control arm. Quality of life, nursing convenience, patient time spent in the infusion suite, and cost data, collected before and after paclitaxel premedication discontinuation also would have been of interest. A small number (15%) of patients included in the primary analysis received 175 mg/m² doses, and although our study was not powered to look at differences between paclitaxel doses, this approach appears to be applicable regardless of paclitaxel dose. The upper limit of the 95% CI (5.3%) exceeds what was previously stated as an acceptable rate of rescue medication usage (5%), however this can be attributed to sample size. If three more subjects would have been included in the primary analysis, then the upper bound of the one-sided 95% CI would have been 5.0%; recall that six patients not included in primary analysis had premiedications resumed in later cycles despite not experiencing an infusion hypersensitivity reaction after paclitaxel premedications were stopped. As the incidence of rescue medication usage in this trial was 0%, these results support the research hypothesis.

As the usage of weekly paclitaxel administration has increased due to improved efficacy and/or less toxicity, the necessity for repeated doses of premedications to prevent infusion hypersensitivity reactions with every dose and the safety of discontinuing these premedications are relevant questions. Hence, our study is important given the simplified approach that prospectively explored stopping premedications after two doses.

In summary, these results showed no use of rescue medication to treat infusion hypersensitivity reactions in 55 patients receiving varying doses and schedules of paclitaxel after premedications were discontinued, with a 95% CI of 0–5.3%. Based on these results, the standard practice of premedicating patients prior to every dose of paclitaxel may include the option of discontinuing premedications with the third and subsequent doses in patients who had not experienced a prior infusion hypersensitivity reaction. This approach looks promising but must be validated with a larger, prospective, randomized trial. Subsequent prospective trials should also include validated questionnaires to assess the side effects of standard premedications and the degree of interference that these symptoms cause on quality of life.

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