

Retrospective evaluation of weekly paclitaxel hypersensitivity reactions reported utilizing an electronic medical record system at a tertiary cancer center

Lincy S. Lal · Donna L. Gerber · Jason Lau · William Dana

Received: 14 October 2008 / Accepted: 20 January 2009
© Springer-Verlag 2009

Abstract

Objectives This is a retrospective observational study evaluating hypersensitivity reactions captured by an electronic medical record (EMR) system for weekly paclitaxel infusions.

Materials and methods The study evaluates the demographics, co-morbidities, premedications, chemotherapy agents, and postmedications of patients reporting a hypersensitivity reaction to weekly infusions of paclitaxel at a major cancer center, from June 2006 to December 2007. Data were analyzed using descriptive statistics and logistic regression. *P* values <0.05 were considered significant.

Results There were 51 hypersensitivity reactions in 36 patients during this time period that were documented in the allergy section of the EMR. Reactions occurred in patients

with an average age of 55 years (SD=10.77); 47 (92%) of the reactions occurred in females, and 42 (82%) of the reactions occurred with orders on the breast medical/surgical service. Thirty-two (63%) reactions occurred with either the first or second dose of weekly paclitaxel infusion. The most common premedication was dexamethasone (50 infusions), followed by diphenhydramine (18 infusions), and cimetidine (14 infusions). Thirty-three (65%) infusions had only one premedication. Postreaction, 41 (80%) cases had diphenhydramine and 30 (59%) cases had hydrocortisone administered prior to restarting the infusion. Logistic regression analysis did not indicate any relationship between history of previous allergies, hypertension, coronary disease, or chronic obstructive pulmonary disease and the number of premedications.

Conclusions The results indicate that there is substantial variability in the type and number of premedications utilized in the management of paclitaxel hypersensitivity reactions. Interventions are needed to decrease the rate of hypersensitivity reactions from weekly paclitaxel infusions.

Keywords Hypersensitivity reactions · Weekly paclitaxel · Premedications

L. S. Lal (✉) · J. Lau

Division of Pharmacy, Drug Use Policy and Pharmacoeconomics,
University of Texas M. D. Anderson Cancer Center,
Unit 706,
Houston, TX, USA
e-mail: llal@mdanderson.org

J. Lau

e-mail: jlau@mdanderson.org

D. L. Gerber

Division of Nursing,
University of Texas M.D. Anderson Cancer Center,
Unit 82,
Houston, TX, USA
e-mail: dgerber@mdanderson.org

W. Dana

Pharmacy Programs, Division of Pharmacy,
Drug Use Policy and Pharmacoeconomics,
University of Texas M. D. Anderson Cancer Center,
Unit 90,
Houston, TX, USA
e-mail: wdana@mdanderson.org

Introduction

Paclitaxel is a commonly utilized anticancer agent for the treatment of various solid tumors, including breast, ovarian, peritoneal, gastric, and non-small-cell lung cancer [10, 11]. The administration of paclitaxel is complicated by hypersensitivity reactions (HSRs), including bronchospasm, dyspnea, hypotension/hypertension, shortness of breath, chest pain/tightness, flushing, wheezing, anxiety, and urticaria, which has earned the drug a black box (the most

severe level) warning by the Food and Drug Administration, the drug approval and regulation body in the USA [14]. The cause of the HSR is not fully understood, though direct interaction with mast cells and basophils, immunoglobulin-E-mediated responses, sensory nerve peptide interaction, and even secondary involvement of the vehicle, polyoxyethylated castor oil, have all been postulated [5, 12, 15]. The actual incidence of paclitaxel HSRs is quite high, ranging from 8% to 45%, with severe reactions occurring in 2–4% of patients [14]. Paclitaxel is initially approved to be administered every 3 weeks and, therefore, much of the hypersensitivity reaction information is available for the higher doses usually administered at this schedule. However, currently, weekly paclitaxel, which is a lower dose, is now utilized in many of the cancers, including breast, ovarian, and non-small-cell lung cancer [1, 2, 6, 13]. There is very limited evidence on HSRs, as well as the premedications for weekly paclitaxel infusions and this paper seeks to increase the documentation of these reactions in the literature [8, 10, 16].

The impact of inappropriate management of hypersensitivity-related adverse drug reactions (ADRs) include: negative experience for the patient during the infusion, discontinuation of necessary treatment, and increased use of resources and costs [7]. Therefore, management of HSRs requires a process for reporting, monitoring, preventing, and managing the symptoms. For a long period of time, health care professionals have been utilizing a paper tracking system to determine the rates of all ADRs in health care institutions. However, recent technological advancements in capturing health care encounter events utilizing the electronic medical record (EMR) system make it a viable option to report and monitor the occurrence of adverse drug reactions, including hypersensitivity reactions. The primary objective of this retrospective observational study is to evaluate the HSRs captured by an EMR system for weekly paclitaxel infusions at a major tertiary cancer center in the US.

Materials and methods

The study was conducted at the University of Texas M. D. Anderson Cancer Center in Houston, TX, USA. All adverse events reported for paclitaxel were captured with an EMR reporting system from June, 2006 to December, 2007. The EMR system captures both inpatient and ambulatory clinic adult and pediatric patient data and the adverse reactions are entered into the system at the time of occurrence or within 72 h by nursing staff at the hospital. The detailed reports are generated on a weekly basis for review and analysis by the pharmacy's Drug Information Department and presented monthly to the institution's Pharmacy and Therapeutics Committee. All data were verified through the

actual medical chart nursing and physician records and all duplicate reports were deleted. For the purpose of this study, the following data were collected: patient demographics of age and gender, co-morbidities of hypertension, coronary artery disease or myocardial infarction, and chronic obstructive pulmonary disorder, premedications, chemotherapy agents, posthypersensitivity management reactions, the times of administration of the premedications, and the rates of the paclitaxel infusion.

The data were analyzed by descriptive statistics with the number of reactions used as the denominator. Univariate logistic regression was utilized to determine predictors for number of premedications and for use of diphenhydramine as a premedication, and the following variables were tested: age; gender; history of previous documented allergy, the number of paclitaxel infusion, and the presence of co-morbidities of interest. *P* value <0.05 was considered to be statistically significant. The study was conducted as part of a performance improvement program, called the Clinical Safety and Effectiveness (CS&E) Education Program, and served as the project for fulfilling the requirements for satisfactory completion of the program. It was approved by the committee responsible for overseeing the CS&E performance improvement projects.

Results

During the study period, 51 reactions in 36 patients were reported as an HSR in the EMR system. The average age of the study population was 55 years (SD10.7), with females experiencing 92% (47/51) of the total reactions. Breast medical and breast surgical departments represented 82% (42/51) of the reaction reports in 28 patients, followed by thoracic medicine at 8% (4/51). Ninety-two percent (47/51) of the reactions occurred in the ambulatory treatment center and not in an inpatient setting. Five (10%) of the reactions occurred in patients who had documentation in the medical chart that they were allergic to paclitaxel already, while 29 (57%) reactions occurred in patients who did not have any documented allergies. During the study period, an average of 193 unique patients received weekly paclitaxel infusions on a monthly basis, for a total of 3,476 patients during the study duration, accounting for a rate of 1.5% HSRs.

Table 1 lists the types of reactions experienced by the patients. The reaction signs and symptoms are consistent with HSRs of grades 2 and 3 according to the grading available from the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3.0 [9]. A weekly dose of 80 mg/m² was the one utilized in the majority of cases.

Table 2 and Fig. 1 indicate the characteristics of the paclitaxel infusions and the associated premedications. The

Table 1 Hypersensitivity reaction (HSR) signs and symptoms to weekly paclitaxel infusions

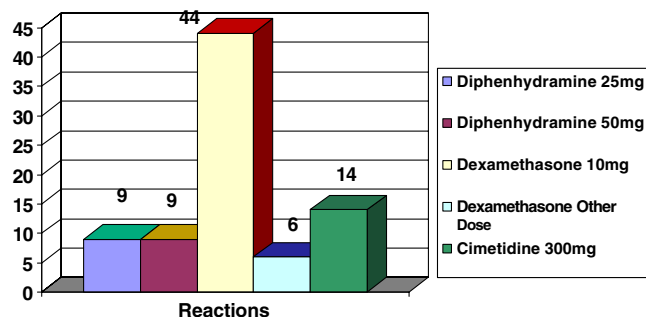
Chills	Hypotension
Flushing	Hypertension
Hot flashes	Heartburn
Back pain	Abdominal pain
Chest pain	Lower-extremity pain
Chest tightness	Cough
Shortness of breath	Nausea
Anxiety	Vomiting
Diaphoresis	Rash/Urticaria/Hives
Headache	Wheezing

majority (49%) of the reactions occurred with the first dose, with the second and third dose being responsible for 14% and 16%, respectively. Hypertension was a co-morbid diagnosis in patients experiencing 47% of the reactions

Table 2 Characteristics of the weekly paclitaxel infusions and associated premedications

Characteristics	N=51 (%)
Paclitaxel infusion number at time of HSR	
First	25 (49.02)
Second	7 (13.73)
Third	8 (15.69)
Fourth	6 (11.76)
Fifth	3 (5.88)
Sixth	2 (3.92)
Co-morbidities present in patients at time of infusion	
Hypertension (HTN)	24 (47.06)
Coronary artery disease (CAD)/myocardial infarction (MI)	3 (5.88%)
Chronic obstructive pulmonary disease (COPD)	2 (3.92%)
Type and number of chemotherapy	
Weekly paclitaxel only	44 (86.27)
Weekly paclitaxel in combination with other chemotherapy	7 (13.73)
Number of premedications	
One	33 (64.71)
Two	5 (9.80)
Three	13 (25.50)
Types of premedications	
Dexamethasone	50 (98.04)
Diphenhydramine	18 (35.29)
Cimetidine	14 (27.45)
Timing of premedications	
Ordered 30 min prior	50 (98.04)
Ordered 15–30 min prior	1 (1.96)
Time actually administered prior to paclitaxel dose: minutes (SD)	63 (43.73)
Initial paclitaxel infusion rates	
250 mL/h	45 (88.24)
167 mL/hr	2 (3.92)
Other	4 (7.84)

SD standard deviation

**Fig. 1** Specific types of premedications administered for the weekly paclitaxel infusions

and paclitaxel was the only chemotherapeutic agent in 86% of the reactions. The majority (65%) of the infusions were only premedicated with one medication, and dexamethasone was the most frequent agent of choice for premedication in 50 (98%) of the reactions, followed by diphenhydramine utilized in 18 (35%) of the reactions. The majority of the premedications were ordered 30 min prior to the paclitaxel dose in 50 of the reactions, while the actual time of administration was 63 min (SD 44 min). Figure 1 illustrates the specific types and doses of medications utilized in the premedication orders. Dexamethasone 10 mg was the most common drug and dosage.

Table 3 lists the characteristics of the postreaction outcomes and the interventions, in terms of medications and infusion rates. At the first sign of the HSR, 50 (98%) of the infusions were stopped, while one patient experiencing the reaction continued to receive the paclitaxel infusion. After a period of time, the infusion was restarted in 47

Table 3 Characteristics of the postreaction outcomes and interventions

Characteristics	N=51 (%)
Post reaction infusion outcome	
Infusion stopped at time of reaction	50 (98.04)
Infusion restarted after a period of time	47 (92.16)
Postreaction paclitaxel infusion rates	
Lower	20 (39.22)
Unknown	25 (49.02)
Same	3 (5.88)
Not applicable (discontinued infusion)	3 (5.88)
Number of postmedications for treatment of signs and symptoms	
Zero	1 (1.96)
One	21 (41.18)
Two	24 (47.06)
Three	5 (9.80)
Types of postmedications for treatment of signs and symptoms	
Diphenhydramine	41 (80.39)
Hydrocortisone	30 (58.82)
Cimetidine	7 (13.73)
Other	5 (9.80)

(92%) of the instances. In 20 (39%) of the infusions where the reactions occurred, the infusion was restarted at a lower rate, while, in three of the cases, the infusion was restarted at the same rate and, in 25 of the cases, the reinstituted rate is unknown. Three patients completely discontinued paclitaxel infusion when they experienced the HSR. The number of the medications given to manage the HSR ranged from zero to three, with the majority being administered two medications for 24 of the reactions (47%), which happen to be diphenhydramine and hydrocortisone primarily.

Univariate logistic regression method was employed to determine if there were any predictors associated with the number of premedications administered and for including diphenhydramine as a premedication, but the analysis did not result in any significant findings.

Discussion and conclusions

Hypersensitivity reactions to paclitaxel are widely published. However, there is paucity in the available information concerning HSR specifically to weekly infusions of paclitaxel. It is evident from this study that, even with a lower dose than commonly administered for the 3-week regimen, there are reactions for which appropriate management is necessary. In our current study which focused on electronic entry of HSRs, we encountered a rate of 1.5% over the study period, which the authors feel is consistent with two other published studies for weekly infusions but lower than the rate seen by Quock et al. [8, 10, 16]. It was also noted that a large percentage of the reactions occurred in instances with existing hypertension. One reason for this finding could be that there was a nursing policy to document blood pressure readings prepaclitaxel and postpaclitaxel infusions, due to the known adverse event of hypotension with paclitaxel, and the increase in blood pressure was captured due to this aggressive monitoring. However, there are also studies that illustrate that breast cancer patients may be at higher risk of hypertension due to the disease itself and the various chemotherapeutics and hormonal products they have taken during the course of the disease [3, 4].

It is important to note that capturing adverse drug reactions through an electronic medical chart record is a relatively new process, especially when compared to the old-fashioned paper method. Previously, the nurse or other health care professionals needed to submit a separate adverse drug reaction paper form to the pharmacy for the capture and monitoring of ADRs, including HSRs, at this institution. However, now as the health care professional is conducting the patient evaluation, the event is captured at each encounter using the EMR system. The pharmacy drug information personnel receive a report of these entries on a weekly basis, thus eliminating the need for the extra

paperwork and decreasing the potential for missing reaction reports. During each subsequent patient encounter, the information is updated as needed into the EMR; all updates are also included in the weekly reports. The EMR provides a mechanism to overcome the paucity in reporting of ADRs to the pharmacy department, which is responsible for actively monitoring and evaluating the ADRs occurring at a health care institution; however, it does not at this time provide a means to concurrently conduct the evaluation process to determine causality, severity, and preventability. This process still needs to be conducted by pharmacists on a case-by-case basis.

While the majority of these reactions appear to be with the first dose and with one premedication, there is evidence that the immune system sensitivity exists in subsequent doses and even with two or three premedications. Fifteen of the reactions reoccurred in patients who already experienced an earlier HSR, indicating the need for intervention in subsequent infusions, either by increasing the number of premedications or initiating a desensitization protocol in patients who experience at least one reaction, depending on the number of premedications at the time of the first reaction.

Based on this study, the institution is doing a prospective study evaluating different types and amount of premedications to determine a standard premedication protocol for all weekly paclitaxel medications. Since there are additional costs and side effects, such as hyperglycemia and opportunistic infections from steroid use, one of the commonly used premedications, it is essential that the most efficacious, but, at the same time, the ones with the least adverse event potential, and the most consistently cost-effective agents be utilized for the premedication scheme. Unfortunately, none of the covariates analyzed in the logistic regression was associated with the probability of utilizing more premedications in the study population or to specifically adding diphenhydramine, to develop a high-risk classification for potential high-level management preemptively. At the same time, a standardized postreaction management order set has been finalized for all patients experiencing HSR from all types of chemotherapeutic agents, including paclitaxel within the institution, to limit the deleterious effects of the HSR once it has occurred.

Acknowledgements Presented as an invited lecture at the Supportive Care in Cancer MASCC/ISOO 2008 International Symposium in Houston, TX, USA on June 26–28, 2008. No funding was available for this study.

References

1. Akerly W, Sikov WM, Cummings F et al (1997) Weekly high-dose paclitaxel in metastatic and locally advanced breast cancer. A preliminary report. *Semin Oncol* 24:87–90

2. Chang AY, Boros L, Asbury R et al (1997) Dose-escalation study of weekly 1-hour paclitaxel administration in patients with refractory cancers. *Semin Oncol* 24:69–71
3. Dyer AR, Stamler J, Berkson DM et al (1975) High blood-pressure: a risk factor for cancer mortality? *Lancet* 1:1051–1056. doi:[10.1016/S0140-6736\(75\)91826-7](https://doi.org/10.1016/S0140-6736(75)91826-7)
4. Goon PKY, Messerli FH, Lip GYH (2006) Hypertension and breast cancer: an association revisited? *J Hum Hypertens* 20:722–724. doi:[10.1038/sj.jhh.1002053](https://doi.org/10.1038/sj.jhh.1002053)
5. Itoh Y, Sendo T, Hirakawa T et al (2004) Role of sensory nerve peptides rather than mast cell histamine in paclitaxel hypersensitivity. *Am J Respir Crit Care Med* 169:113–119. doi:[10.1164/rccm.200307-901OC](https://doi.org/10.1164/rccm.200307-901OC)
6. Lau DHM, Ryu J, Gandara D et al (1999) Concurrent twice weekly paclitaxel and thoracic irradiation for stage III non-small cell lung cancer. *Semin Radiat Oncol* 9:117–120
7. Lenz HJ (2007) Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 12:601–609. doi:[10.1634/theoncologist.12-5-601](https://doi.org/10.1634/theoncologist.12-5-601)
8. Milani A, DePas T, Noberasco C et al (2007) A 15-min premedication for 1-h paclitaxel infusion: optimizing patients' care. *Lung Cancer* 58:300–301. doi:[10.1016/j.lungcan.2007.08.009](https://doi.org/10.1016/j.lungcan.2007.08.009)
9. National Cancer Institute (2006) Common terminology criteria for adverse events v3.0 (CTCAE). National Cancer Institute, Bethesda
10. Quock J, Dea G, Tanaka M et al (2002) Premedication strategy for weekly paclitaxel. *Cancer Invest* 20:666–672. doi:[10.1081/CNV-120003535](https://doi.org/10.1081/CNV-120003535)
11. Rowinsky EK, Onetto N, Canetta RM et al (1992) Taxol: the first of the taxanes, an important new class of antitumor agents. *Semin Oncol* 19:646–662
12. Ruiz-Casado A, Calzas J, Garcia J et al (2006) Life-threatening adverse drug reaction to paclitaxel. Postmarketing surveillance. *Clin Transl Oncol* 8:60–61. doi:[10.1007/s12094-006-0098-5](https://doi.org/10.1007/s12094-006-0098-5)
13. Sparano JA, Wang M, Martino D et al (2008) Weekly paclitaxel in the adjuvant treatment of breast cancer. *N Engl J Med* 358:1663–671
14. University of Texas M. D. Anderson (2008) Paclitaxel. Lexi-Comp ONLINE, Hudson
15. Weiss RB, Donehower RC, Wiernik PH et al (1990) Hypersensitivity reaction from taxol. *J Clin Oncol* 7:1263–1268
16. Zidan J, Hussein O, Abzah A et al (2008) Oral premedication for the prevention of hypersensitivity reactions to paclitaxel. *Med Oncol* 25:274–278