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Impact of institutional interventions on the rate of paclitaxel hypersensitivity reactions

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Abstract

Purpose Paclitaxel is associated with hypersensitivity reactions (HSRs). Intravenous premedication regimens have been devised to decrease the incidence and severity of HSRs. At our institution, intravenous dexamethasone, oral histamine 1 receptor antagonists (H1RA) and histamine 2 receptor antagonists (H2RA) were adopted as standard. Standardizations were implemented for consistent premedication use in all disease states. The purpose of this retrospective study was to compare the incidence and severity of HSRs before and after standardization.

Methods Patients who received paclitaxel from April 20, 2018 to December 8, 2020 having a HSR were included in analysis. An infusion was flagged for review if a rescue medication was administered after the start of paclitaxel infusion. Incidence of all HSR prior to and post standardization were compared. A subgroup analysis of patients receiving paclitaxel for the first and second time was performed.

Results There were 3581 infusions in the pre-standardization group and 1179 infusions in the post-standardization group. After review, 100 HSRs pre-standardization and 38 HSRs post-standardization were confirmed reactions. The rate of overall HSRs was 2.9% in the pre-standardization group and 3.3% in the post-standardization group (p=0.48). HSRs, during the first and second doses of paclitaxel, occurred in 10.2% of the pre-standardization and 8.5% in the post-standardization group (p=0.55).

Conclusions This retrospective interventional study demonstrated that same-day intravenous dexamethasone, oral H1RA, and oral H2RA is a safe premedication regimen for paclitaxel. No change in severity of reactions was seen. Overall, better adherence to premedication administration was seen post standardization.

Introduction

Paclitaxel (Taxol®) is FDA approved and used for the treatment of common types of cancers such as breast cancer and ovarian cancer.[1] A black box warning for anaphylaxis and severe hypersensitivity reactions (HSRs) is listed in the package insert. Paclitaxel has poor solubility and is commercially compounded in Cremophor EL®, an emulsifying agent that play a role in the pathogenesis of HSRs.[2] Cremophor EL® is thought to cause complement activation leading to HSRs and, hence the need for premedication.[3] Three premedications are required prior to paclitaxel infusion to reduce the severity of and prevent HSRs. A histamine 1 receptor antagonist (H1RA) and histamine 2 receptor antagonist (H2RA) should be administered at least 30 minutes prior to the paclitaxel infusion. The package insert recommends dexamethasone administration approximately 12 and 6 hours prior to paclitaxel; however, intravenous dexamethasone on the day of infusion 30 minutes to paclitaxel infusion has been validated in the literature as effective and commonly employed in clinical practice.[4, 5] HSRs can still occur despite recommended premedication.

HSR can present with cutaneous eruptions, lower back pain, flushing, dyspnea, chest pain, hypotension and throat tightness that vary in severity.[6] Management of hypersensitivity reactions involves stopping

the infusion and employing symptom management.[7, 8] Agents used as premedications can be administered for reactive symptom management in paclitaxel HSRs. Further symptom management with vasopressors, fluid boluses, bronchodilators, and epinephrine can be used in severe cases.[9] In recent prospective trials, institutions have reported HSRs of all grades occurring in 6% or less in their population.[10–12] Nearly 95% of reactions to the general class of taxanes occurred during the first or second infusion.[13] Additionally, patients who have had a history of reactions to previous courses of paclitaxel, presence of respiratory dysfunction, obesity, and postmenopausal status are at elevated risk for paclitaxel HSRs.[14]

At our National Cancer Institute designated cancer center, a multidisciplinary group was developed to evaluate paclitaxel premedication regimens to identify opportunities for improvement after concerns were raised from nursing staff regarding unclear language in order sets leading to variable pre-medication practices. An internal review found inconsistencies among paclitaxel order sets between cancer disease groups on paclitaxel orders including variation in timing and route, varied nursing premedication practices for subsequent doses due to “may hold if no previous reaction” verbiage, and the use of syringe pumps to administer IV premedications leading to variable timing between the end of premedications and the start of paclitaxel. Changes were made to order sets based on published literature, institutional data, and recommendations of a multidisciplinary group that included clinical pharmacists, nursing, and providers. Our institution implemented universal oral administration of H1RAs and H2RAs, as consistent timing would allow for absorption and distribution of these medications. The oral route has the advantage of lower costs and less nursing time. The purpose of this retrospective study was to compare the rates of reactions pre- and post-standardization interventions to understand the impact of the changes.

Methods

This was a retrospective single-center study conducted at the Fred Hutchison Cancer Center in Seattle, WA, USA. This study was approved by the University of Washington Human Subjects Division Institutional Review Board with a waiver of consent granted.

Data Collection

Patients who received paclitaxel from April 20, 2018 to December 8, 2020 identified by paclitaxel orders were included in the overall analysis. The standard practice is that all chemotherapies are ordered through an electronic order set to ensure safe ordering, appropriate pharmacist and nursing verification, and documentation. HSRs were identified by the administration of H1RA (diphenhydramine), H2RA (famotidine), steroids (methylprednisolone or hydrocortisone), and/or epinephrine after the start of the paclitaxel infusion. Finally, a reaction to paclitaxel was confirmed through nursing infusion notes (all infusions are documented by a nurse in the medical chart even if no reaction occurred). System-wide changes were made between April 20, 2020 and April 21, 2020. The pre-standardization group were patients who received paclitaxel from April 20, 2018 to April 20, 2020. The post-standardization group

were patients who received paclitaxel from April 21, 2020 to December 8, 2020. Patients were excluded if “rescue medication” was given for reasons other than hypersensitivity reactions. Patients were counted if they had a HSR reaction, and repeat reactions identified from a repeat patient was excluded from analysis. Type of malignancy was obtained. Infusion reaction severity was analyzed and graded based on Common Terminology Criteria of Adverse Events 5.0.[15]

Institutional interventions

Prior to standardization, there were differing time intervals between the end of administration of premedications and the start of paclitaxel. In reviewing 42 paclitaxel order sets across the center, premedication timing varied between 15–30 minutes pre-paclitaxel infusion depending on the disease state group’s decision. Additionally, the use of syringe pumps for non-standardized dilutions and rates created even more variability.

Post standardization, all order sets had clear language outlining the need for 30 minutes to elapse between the end of administration of premedications and the start of paclitaxel infusion. Additionally, there were nursing educational sessions and computerized provider order entry changes to use oral administration for H1RAs and H2RAs as a default. Additionally, syringe pumps were removed from infusion areas.

The efficacy of oral versus intravenous diphenhydramine for mitigating HSRs was not firmly established in the medical literature at the beginning of the study period. Due to a national intravenous diphenhydramine shortage, oral diphenhydramine was adopted as a premedication. Understanding this “natural experiment” was part of the rationale for this study. Our institution defaulted all order sets to the oral route of administration of diphenhydramine and famotidine. For dexamethasone, previous studies looked at oral dexamethasone have compared the two-dose oral strategy versus same day intravenous.[5, 16] At our instituition, dexamethasone was kept as a one-time intravenous dose as the two dose oral strategy is dependent on patient adherence. Nursing workload was decreased with decreased medication manipulation and stocking all premedications in automated dispensing cabinets. Additionally, there was a decreased cost to the institution and cost savings passed on to patients and insurers.

Implementation of mandatory premedications with the second infusion of weekly paclitaxel was clarified in nursing communications and defaulted in CPOE. Prior to standardization, the first paclitaxel infusion had mandatory premedications. On subsequent infusions, premedications were only mandated if the patient had reacted to previous infusions. On a preliminary, internal data review, 76% of the patients who reacted to the 2nd dose of paclitaxel did not react to their 1st infusion. Paclitaxel premedications are recommended for all paclitaxel infusions per the manufacturer. However, it has been established that the majority of HSRs will occur during the first and second paclitaxel infusions.[13] Based on the literature, our institutional policy mandated premedications for the first two paclitaxel administrations, and premedications were removed for patients without reactions as this had no impact on incidence of HSR or increase of rescue medications in previous studies.[12, 17]

Further clarification was made to verbiage in the nursing order communication for premedications. The order stated, “may hold if no reaction to previous doses” and was interpreted differently by nursing staff in different clinics leading to variable practices including holding all, none, or some premedications. Nursing order communication was changed to “hold if no reaction to previous doses of paclitaxel.” Conversely, throughout all clinics, the standard practice of premedication administration for any history of HSRs with paclitaxel was adopted. All these changes were made to reduce inter- and intra-patient variability of supportive care measures.

Results

The primary outcome was to compare the overall incidence of paclitaxel hypersensitivity reactions and rate of reactions for first and second infusions prior to and after implementation of the previously outlined standardization measures. Secondary outcomes included severity of hypersensitivity reactions, rescue medications administered, characterization of premedication regimen administered to those who reacted, and cost savings. The Fisher’s exact test was used to compare rates of hypersensitivity reactions pre- and post-intervention. Categorical variables were evaluated with the $\chi 2$ or Fisher’s exact test as appropriate.

In total, there were 3581 infusions in the pre-standardization group and 1179 infusions in the post standardization group. Of these, 159 HSRs in the pre- standardization group and 57 HSRs in the post-standardization group were flagged for review. After retrospective chart review, 100 HSRs and 38 HSRs were confirmed, pre-standardization and post-standardization respectively. A Fisher’s exact test resulted in no statistically significant difference in HSRs between the pre-standardization and post-standardization groups ($p = 0.55$). As shown in Table 2, the rate of any HSR was 2.9% in the pre-standardization group and 3.3% in the post-standardization group. Specifically looking at the first and second paclitaxel infusion reactions, the rate of HSR was 9.7% in the pre-standardization group and 8.2% post-standardization group, with no statistically significant difference detected ($p = 0.55$). A contingency matrix is shown in Table 3 for the initial 2 paclitaxel infusion reaction incidence.

Table 1
Contingency table comparing all infusion reactions

	Pre-standardization	Post-standardization	Totals
Included flagged reactions	100 (2.9%)	38 (3.3%)	138
No reaction	3399 (97.1%)	1121 (96.7%)	4520
Total paclitaxel infusions	3499	1159	4658
Fisher’s exact two-tailed test **p = 0.48.** (Patients who had multiple reactions were removed from the analysis and were counted only once)			

Table 2
Contingency table comparing first and second infusion HSRs

	Pre-standardization	Post-standardization	Totals
Included flagged reactions	84 (9.7%)	22 (8.2%)	106
No reaction	781 (90.3%)	246 (91.8%)	1027
Total first and second paclitaxel infusions	865	268	1133
Fisher's exact two-tailed test **p = 0.55**			

HSR infusion characteristics are listed in Table 3. After review, 100 (2.9%) HSRs pre-standardization and 38 (3.3%) HSRs post-standardization were confirmed with nursing administration notes. The mean age of patients who experienced HSRs were 52 and 53 years old, in the pre-standardization and post-standardization groups, respectively. There were 84 (9.7%) HSRs pre-standardization and 22 (8.2%) HSRs post-standardization that occurred in the first and second paclitaxel infusion. A majority of the patients received weekly paclitaxel for treatment of breast cancer.

Table 3
HSR Infusion Characteristics

	Prior Standardization (n = 100)	**Post Standardization (n = 38)**
Age in years, mean (range)	52 (25–80)	53 (31–88)
Female, *N* (%)	77 (54.6%)	33 (68.8%)
Infusion Number		
First Infusion, *N* (%)	50 (50%)	8 (23.5%)
Second Infusion, *N* (%)	34 (34%)	14 (41.2%)
Third Infusion, *N* (%)	8 (8%)	7 (20.6%)
≥Fourth Infusion, *N* (%)	8 (8%)	9 (26.5%)
Malignancy		
Breast	63 (63%)	21 (55.3%)
Non-small cell lung cancer	12 (12%)	2 (5.3%)
Head and Neck	6 (6%)	1 (2.6%)
Ovarian	2 (2%)	2 (5.3%)
Other*	17 (17%)	12 (31.6%)
*Other malignancies encompass colorectal, gastroesophageal, pancreatic, sarcoma, thyroid, neuroendocrine, small cell lung cancer		

Most hypersensitivity reactions were grade 2 in both groups. There were 4 cases of grade 3 infusion reactions occurring in the prior to standardization group. There were 2 cases of grade 3 and 1 case of a grade 4 infusion reaction in the post standardization group, as shown in Table 4. No reactions were reported as grade 1 or grade 5.

Table 4
Severity of infusion reaction based on CTCAE 5.0

	Prior Standardization (n = 100)	Post Standardization (n = 38)
Grade 1	0	0
Grade 2	96 (96%)	35 (92.1%)
Grade 3	4 (4%)	2 (5.3%)
Grade 4	0	1 (2.6%)
Grade 5	0	0

Characterization of premedication prescribing habits during the first and second infusions are depicted in Table 5. An increased use of the oral formulations of diphenhydramine and famotidine were seen post-standardization. An increase in utilization of oral diphenhydramine from 15.7–78.5% was found. Additionally, there was increased use of oral famotidine from 42–78.9% post-standardization. Fewer patients were given no premedication administration post-standardization. A cost comparison is presented in Table 6.

Table 5
Characterization of administration of premedications for first and second infusions

	Prior standardization (n = 883)			Post standardization (n = 270)		
N (%)	IV	PO	None*	IV	PO	None*
Diphenhydramine	506 (57.3%)	139 (15.7%)	238 (27%)	29 (10.7%)	212 (78.5%)	29 (10.7%)
Famotidine	264 (29.9%)	371 (42%)	248 (28.1%)	30 (11.1%)	213 (78.9%)	27 (10%)
Dexamethasone	672 (76.1%)	0 (0%)	211 (23.9%)	242 (89.6%)	0 (0%)	28 (10.4%)
No infusions were excluded for analysis of premedication regimen to better categorize adoption of institutional standardization for all first and second infusions.						
*Premedications that were administered more than 1 hour before administration were flagged as none in both prior and post standardization group. A percentage decrease was still seen post standardization.						

Table 6
Drug Pricing and comparison of drug regimen prior to standardization and post

Prior to Standardization		Post Standardization	
Diphenhydramine 25 mg IV	$0.27	Diphenhydramine 25 mg PO	$0.03
Famotidine 20 mg IV	$0.27	Famotidine 20 mg PO	$0.06

Discussion

The use of oral H1RAs and H2RAs have not been studied for paclitaxel premedication regimens, and intravenous premedications are the standard of care. Our study shows no clinical or statistically significant difference in the severity or incidence of HSRs with oral diphenhydramine and famotidine. Institutional standardization resulted in decreased incidence of first and second infusion HSRs, although not statistically significant.

There was an increased use of oral premedications after the numerous interventions and standardization efforts. Oral administration prevents the use of syringe pumps and other means of infusing intravenous medications, improving safety through the ability to precisely time the premedications. This also serves as a cost-saving initiative and results in ease of administration for nursing staff. The cost of premedications can be seen in Table 6 with oral premedication being cheaper than intravenous administration. The multidisciplinary group decided not to move to oral dexamethasone as the only premedication regimens studied for oral dexamethasone are 12 and 6 hours prior to paclitaxel infusions at the time of the study. However, a recent paper by Lansinger et al that looked at steroid premedication in first administration of any type taxane had found no correlation with route or dosing with incidence/severity of HSRs.[18] This paper, in conjunction with our study, may catalyze other institutions to implement entirely oral premedication regimens to aid in reduction in infusion chair time and nursing demand. In addition to removing syringe pumps from infusion areas, the institution developed standard dilution guidelines for IV push medications, including dexamethasone. Due to concerns of perineal pruritis, nursing staff diluted dexamethasone and ran it slowly over a syringe pump. Standardizing the dilution and push time helped alleviate concerns of adverse effects.

Prior to this study, institutional practice required pre-medications for only first dose of weekly paclitaxel, and pre-medications for subsequent infusions were only required if a prior reaction was reported. Our change to requiring pre-medications for first and second doses demonstrated a downward trend in reaction rates. Although the trend is not statistically significant, we believe our sample size post-implementation is not large enough to demonstrate statistical significance. Stopping premedications after the first two infusions without demonstration of reaction in patients may reduce the exposure to systemic glucocorticoids, decreases appointment times/chair time, and aids in convenience of administration of paclitaxel.

The implementation strategy was key to the successful deployment of the interventions. Where possible, the changes were built into workflow processes, removing the need for providers, nursing, or pharmacists to refer to guidelines or policy. To prevent variation in prescribing practices, the oral route was defaulted in the computerized order entry for diphenhydramine and famotidine. Pre-medications for first and second doses were defaulted. Syringe pumps were removed from all infusion areas to prevent use. Nursing staff were educated about all the changes implemented including standard dilution practices. Dedicated nursing education days were used, and competency assessments were completed. A multidisciplinary approach provided a comprehensive outlook of workflow processes and stronger support to implement institutional changes.

Through this retrospective review, a comprehensive review of deviations from our standard practice were performed. There were some patients who received IV premedications in the post-standardization group. This may be explained by legacy order sets with non-standard premedication regimens. Additionally, there may be a subset of patients who are unable to take oral medications, necessitating the need for IV administration. There is a subset of patients in the post-standardization group who did not have documented premedication that may be explained by transferring from an outside institute or re-entry of an order set flagging as a “new” initiation.

A hypersensitivity trigger tool may serve others in identifying and characterizing hypersensitivity for other types of medications. Paclitaxel infusion reactions were flagged when rescue medications were provided to patients after the start of the paclitaxel infusion and confirmed by cross-referencing nursing notes. Nursing documentation is key to ensure the interdisciplinary team’s ability to formulate a plan for the patient, accounting for the severity and management of the HSR. A manual retrospective review was necessary to ensure that the trigger tool reflected a paclitaxel HSR, as paclitaxel is often administered with carboplatin. Carboplatin carries a risk for infusion reactions usually occurring after multiple exposures to the platinum agent.[19, 20] Additionally, this trigger tool is only able to capture infusion reactions grade 2 and above, because of the necessity for administration of an supportive care agent.[15] Overall, using rescue medications as a trigger tool for adverse drug events can be implemented at infusion centers assesses the rates of HSRs to paclitaxel and other agents with unique rescue pharmacotherapeutic agents. This generalization to other medications can help improve workflow processes that may not be easily identified by staff.

There are some limitations to this retrospective trial. Clear documentation was necessary to grade HSRs. Additionally, some treatment plans may have continued past the post intervention date, as an adoption grace period was not implemented. Another limitation is the small sample size of the post-intervention group due to the limited time frame compared pre-implementation group.

In conclusion, this retrospective interventional study demonstrated that same day intravenous dexamethasone, oral H1RA, and oral H2RA is a convenient and safe option for the prevention of paclitaxel HSRs. The study also showed a statistically non-significant decline in 1st and 2nd dose HSRs with the implementation of required pre-medications, improved ability to time pre-medications with the

change to oral administration, and cost savings for diphenhydramine, famotidine, and ondansetron. Dropping pre-medications after 2nd dose of weekly paclitaxel may prove useful in decreasing the systemic exposure to corticosteroid. Additionally, there may be a theoretical benefit with the reduction of line manipulations using an oral premedication regimen. Through multidisciplinary collaboration, standardization of order sets, and education prescribing habits were effectively changed. This study demonstrated the usefulness of a trigger tool to identify workflow improvements in paclitaxel, and the possibility of generalization for other medications that are commonly associated with infusion reactions. More studies are needed to further elucidate if these changes could translate to other clinical outcomes such as infection risk or patient satisfaction.

Declarations

Ethics Approval

This study was approved by the University of Washington Human Subjects Division Institutional Review Board with a waiver of consent granted due the retrospective nature of this study.

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All authors contributed to this retrospective review's design and conception. Manuscript preparation and data analysis were performed by Mark Jao. The first draft of this manuscript was written by Mark Jao and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data available on request from the authors with IRB approval.

Custom code or software application: N/A

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