Safely Stopping Pre-medications in Patients Receiving Paclitaxel: A Randomized Trial

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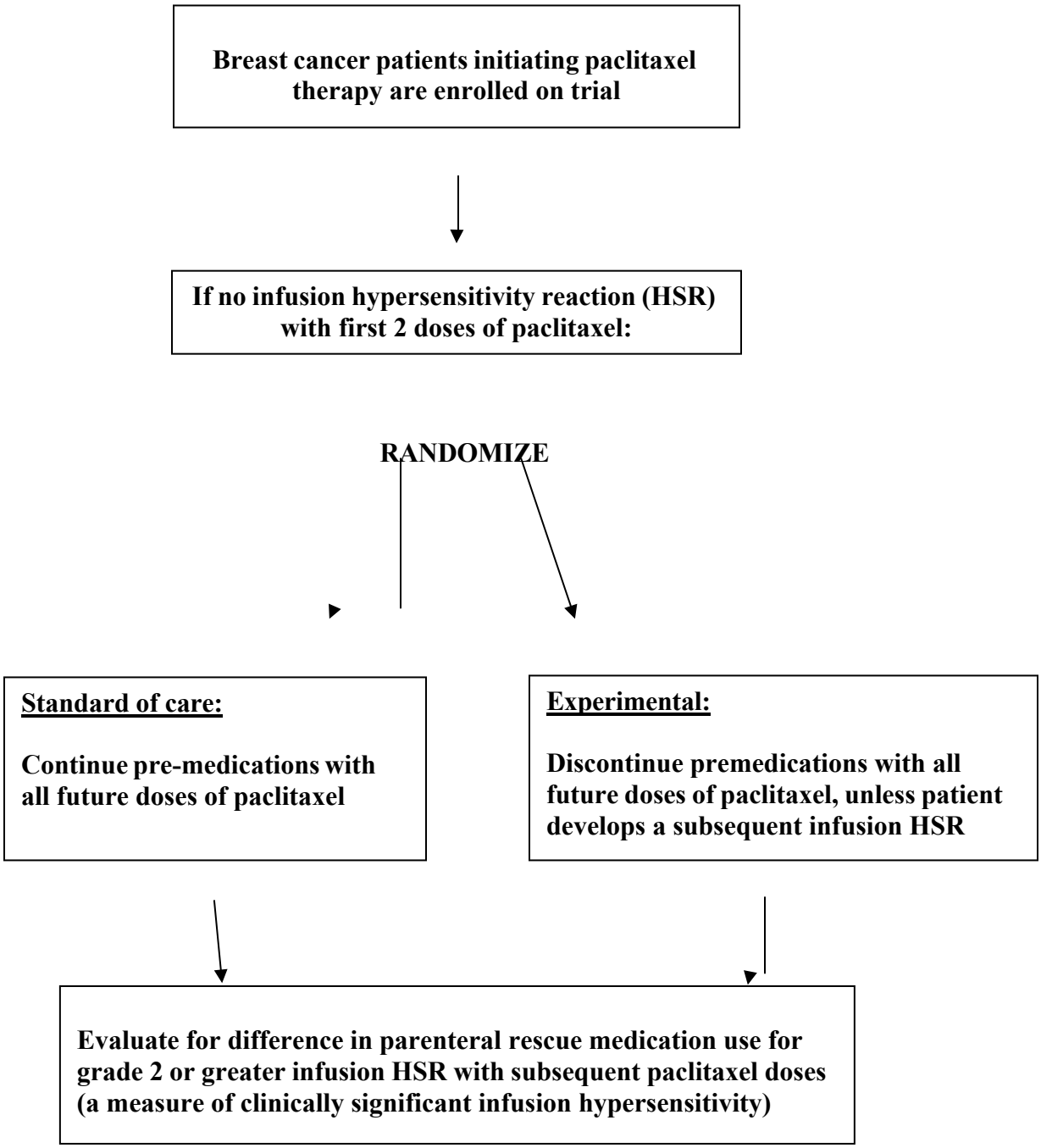
Study Schema:



Stratification Factors

- Weekly paclitaxel vs every 14-day paclitaxel dosing
- Hypersensitivity premedication regimen

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1.0 Objective

The goal of this study is to estimate the difference in rates of infusion hypersensitivity reaction (HSR) requiring parenteral rescue medications following the discontinuation of pre-medications after 2 doses of paclitaxel, compared to continuing premedications, in breast cancer patients who have not experienced an infusion HSR with their first 2 paclitaxel doses.

2.0 Background and Rationale

Paclitaxel is commonly used in a variety of solid tumors, including breast cancer. Due to its hydrophobic properties, paclitaxel is emulsified in polyoxyethylated castor oil (Cremophor El) and ethanol. Paclitaxel (particularly, its solvent cremophor) is known to cause infusion hypersensitivity reactions (HSR). Therefore, patients have been routinely pre-medicated with a steroid (dexamethasone), an H1 antagonist (diphenhydramine), and a H2 antagonist (e.g., famotidine or ranitidine) for HSR prophylaxis before paclitaxel infusions, to mitigate or minimize the severity of the reaction. In early published clinical studies, all grade hypersensitivity reactions occurred in 41% of patients (prior to routine use of premedications) and grade 3 or higher reactions occurred in 2% of patients with the use of a standard pre-medication regimen.[1] Similar grade 3 reaction rates of less than 3% have been reported in patients with breast cancer receiving weekly paclitaxel.

However, there are side-effects and toxicities associated with repeat exposure to this pre-medication regimen. The most frequently used corticosteroid in the prevention of paclitaxel-induced hypersensitivity reactions is dexamethasone, which is among the most potent and long acting of the corticosteroids. With prolonged use of paclitaxel, especially during weekly regimens, patients are exposed to repeat doses of dexamethasone. Side-effects include, but are not limited to, insomnia, gastritis, fluid retention, weight gain, mood changes and immune suppression.[2] Furthermore, the use of parenteral diphenhydramine is commonly associated with drowsiness and can paradoxically cause dystonia and restlessness.[3]

In addition to short term toxicities, use of steroids along with chemotherapy has been associated with potentially increased risk of hyperglycemia, metabolic syndrome, and type II diabetes mellitus. Chemotherapy has been reported to have varying effects on markers of glucose regulation.[4-7] In an observational study of 963 breast cancer patients undergoing chemotherapy, without diagnosed metabolic syndrome or diabetes at baseline, researchers reported that dysregulated glucose metabolism was exacerbated by chemotherapy[4]. Over 70% of women met criteria for metabolic syndrome after four months of chemotherapy. This is a critical problem, considering that metabolic syndrome increases risk for co-morbidities such as cardiovascular disease and diabetes[8] and is associated with increased mortality in women with breast cancer [9]. Although the mechanism by which chemotherapy induces deterioration in glucose metabolism is not completely clear, several studies have postulated that weight gain associated with chemotherapy treatment for breast cancer, promotes development of inflammation and insulin resistant.[10,11] Use of steroids can further exacerbate chemotherapy-associated metabolic effects.[12] Steroids, in combination with chemotherapy, can have profound effects on glucose and insulin.[12,13] These findings may negatively impact clinical outcomes, since increasing insulin levels and insulin resistance are associated with increased recurrence of breast cancer [13] and increased risk of distance recurrence[14].

A growing body of published data suggests that, if a patient has not experienced an infusion HSR after 2 doses of paclitaxel, the chances of having an infusion HSR reaction with future doses is remote. A prospective single arm study was conducted at the Stefanie Spielman Comprehensive Breast Center (SSCBC), Columbus, OH. Seventy patients with stage I-IV breast cancer receiving paclitaxel therapy were enrolled on this trial from August 2009 to March 2010.[15] Fifty-five patients who did not experience a paclitaxel infusion HSR with first 2 doses had all

pre-medications stopped for future doses and were eligible for primary analysis. The incidence of rescue medication use to treat an infusion HSR in these 55 patients was 0% (CI 0-5.4%).[15]

After the publication of this feasibility study, practice patterns changed at SSCBC; patients with breast cancer who had not experienced an infusion HSR after 2 doses of paclitaxel, and who wished to stop receiving paclitaxel pre-medications due to side effects, were commonly permitted to discontinue pre-medications prior to the 3rd and all future paclitaxel doses.

To evaluate this practice change, SSCBC investigators retrospectively reviewed practice patterns between January 2011 and June 2013. During this time period 449 patients were treated with various schedules of paclitaxel and paclitaxel-containing regimens at the SSCBC. Patients were identified through electronic medical record review. The rationale for doing this retrospective study was to assess the use of rescue medications to treat infusion HSR for paclitaxel doses 3 through 6 after the pre-medications were removed following 2 doses of paclitaxel in patients who had not experienced a prior HSR reaction, to better validate our previous findings in a larger population of patients.[16]

Included in this study were patients ≥18 years old who were scheduled to receive at least four doses of paclitaxel as a single chemotherapy agent or in combination with trastuzumab, bevacizumab, gemcitabine, or other drug combinations (excluding cisplatin or carboplatin) for treatment of any stage breast cancer. Patients with chronic medical conditions were allowed in both the prospective and retrospective studies at the SSCBC. Other exclusion criteria included patients who received therapy with a taxane in the previous 12 months, patients in whom paclitaxel was discontinued or changed to a different taxane after 1-2 doses, patients who did not receive premeds with their first 2 doses of paclitaxel and any pre-medications added back into the plan after being removed previously, unless the reason for doing this was from evidence of a paclitaxel–infusion reaction that occurred without premedications.

Of 449 eligible patients, 234 (52.1%) patients met inclusion criteria, while 215 (47.9%) were excluded. Only two of 234 patients (0.8%) required rescue medication to treat a paclitaxel infusion HSR after pre-medications were removed following the 2nd dose of paclitaxel. These results further demonstrated the safety and feasibility of discontinuing pre-medications after 2 doses of paclitaxel in patients who had not experienced a prior HSR reaction.

Other authors have also reported confirmatory findings. Parinyanitikul N et al. recently published a retrospective study of Asian women receiving weekly paclitaxel 80 mg/m2 for early stage breast cancer.[17] Patients received dexamethasone 5 mg IV, diphenhydramine 25 mg IV and ranitidine 50 mg IV pre-medications; if no infusion HSR was seen after the first 2 doses, the dexamethasone was discontinued (the diphenhydramine and ranitidine were continued) for doses 3 through 12. The incidence of HSR in patients who omitted dexamethasone was 6.25% (5 of 81 patients). The authors reported all of these patients were able to be successfully re-challenged with paclitaxel.

Additionally, de Castro Baccarin AL et al. published a small prospective study in women receiving weekly paclitaxel 80 mg/m2 for early stage breast cancer.[18] Patients received dexamethasone 20 mg IV, diphenhydramine 50 mg IV and ranitidine 50 mg IV pre-medications; if no infusion HSR was seen after the first 2 doses, the dexamethasone was discontinued (the diphenhydramine and ranitidine were continued) for doses 3 through 12. The incidence of HSR in patients who omitted dexamethasone was 0% (0 of 25 patients).

It is worth noting that the incidence of infusion HSR and subsequent use of rescue medication in patients who **continue** to receive pre-medications beyond the 2nd dose and beyond, has not been published, to our knowledge.

But, in order to gain insight into this question, we conducted a retrospective chart review of female patients receiving weekly paclitaxel at SSCBC between 2015 and 2020. Patients with any stage breast cancer who had not previously received paclitaxel, and who did NOT have an infusion HSR with their first 2 doses, and who continued premedications aimed at preventing paclitaxel reactions, were examined. Of the first 75 consecutive patients who met this criteria, 3 patients (4%) experienced an infusion HSR that required rescue medication in doses 3 through 12 of paclitaxel.

The above data raise the question of whether it is reasonable to conduct a randomized clinical trial to obtain high-quality evidence to support the discontinuation of pre-medications after 2 doses of paclitaxel compared to continuing pre-medications, which is the standard of care supported by the FDA label for paclitaxel. This is what we will evaluate in this proposed study.

This study is not researching the discontinuation of premeds prior to other taxanes such as docetaxel or cabazitaxel as these drugs may have different premedication requirements and are formulated with a different surfactant than conventional paclitaxel. Paclitaxel albumin-bound, because it is formulated with human albumin and does not contain a surfactant, does not routinely cause infusion hypersensitivity, and therefore has no premedication requirements and will not be included in this research.

If the results of this trial illustrate that the premedications prior to conventional paclitaxel are deemed unnecessary, this should markedly influence clinical practice by reducing chemotherapy administration time, lowering health care costs, decreasing diphenhydramine-induced drowsiness, and decreasing steroid-related toxicities such as agitation, insomnia, bone loss, altered glucose metabolism, and weight gain.

3.0 Eligibility

3.1 Inclusion criteria

3.1.1 Female or male patients scheduled to receive at least 4 doses of weekly paclitaxel 80 mg/m2 or "dose dense paclitaxel" 175 mg/m2 every 14 days, as a single-agent or in combination with trastuzumab, pertuzumab, bevacizumab, pembrolizumab, lapatinib, gemcitabine or other drug combination (excluding cisplatin or carboplatin) for the treatment of any stage, histologically confirmed breast cancer

3.1.2 Ability to complete questionnaires by themselves or with assistance

3.1.3 Life expectancy $\geq$ 6 months

3.1.4 ECOG performance status 0-2

3.1.5 Age $\geq$18

3.1.6 Able to give informed consent

3.1.7 In accordance with standard of care and FDA labeling for paclitaxel, patients must be scheduled to receive prophylactic HSR premedications (IV or oral) consisting of diphenhydramine or cetirizine (histamine-1 (H1) antagonists), dexamethasone (a steroid) and either famotidine, ranitidine, or cimetidine (histamine-2 (H2) antagonists), per institutional guidelines, prior to each of their first 2 doses of paclitaxel.

3.1.8 Patients may enroll, or currently be enrolled in another concurrent clinical trial, including trials with investigational drugs given in combination with paclitaxel, provided the other trial would not prohibit the discontinuation of paclitaxel premedications, and provided the trial would allow for paclitaxel to be administered first in order of infusion.

3.1.9 Intermittent oral steroids for nausea or for acute inflammatory conditions (i.e. methylprednisolone dosepak) and inhaled, intranasal or topical corticosteroids are permitted.

3.2 Exclusion criteria

3.2.1 Patients who have received at least 1 prior lifetime dose of paclitaxel or paclitaxel albumin-bound. (Patients may have received prior lifetime doses of docetaxel or cabazitaxel.)

3.2.2 Patients receiving paclitaxel in combination with carboplatin or cisplatin (due to risk of hypersensitivity with platinum compounds)

3.2.3 History of grade 3 hypersensitivity reaction to cremophor EL containing medications (e.g. paclitaxel, cyclosporine, ixabepilone, teniposide)

3.2.4 Patients receiving therapeutic daily doses of systemic corticosteroids.

3.2.5 Patients who are pregnant or nursing. Paclitaxel is classified by the FDA as "pregnancy category D". Pregnancy testing (urine or blood Hcg) will be done and documented prior to enrollment if pregnancy is clinically suspected.

4.0 Study Design and Methods

4.1 Patient identification and recruitment:

Patients with breast cancer who meet eligibility criteria will be recruited in medical oncology clinics at the Stefanie Spielman Comprehensive Breast Center (SSCBC) of the The James Cancer Hospital at The OSUWMC. After study implementation, the investigators hope to open this trial at additional sites, possibly including the medical oncology clinics from the Minnesota Cancer Clinical Trials Network (MNCCTN) and OSU James Network participating sites. Based upon data obtained from our SSCBC breast medical oncology clinic, there are approximately 2 to 3 patients beginning paclitaxel or paclitaxel-based chemotherapy each week. Some of these patients will be receiving paclitaxel in combination with cisplatin or carboplatin, or may currently be enrolled in another trial that may prohibit changing premedications, and therefore excluded. Estimated duration of the study, based upon projected enrollment of 5-7 eligible patients per month across multiple sites, should be about 18-24 months.

Patients will be screened for eligibility during routine clinic visits by a clinical research coordinator, physician, medical oncology fellow, nurse practitioner, nurse or pharmacist involved in their care. Recruitment will take place only in the context of an established clinical care relationship. Eligible participants will have time to read the study description and consent paperwork as well as meet with a clinical research coordinator to have all questions answered. Any of the investigators can answer questions or review the document with the patient and their family as needed. Eligible patients giving informed consent to participate will be asked to sign the consent form before enrolling in the study. This consent will enable the investigators to review and store in a

password protected database certain characteristics of the patient's cancer history and response to chemotherapy including infusion hypersensitivity reactions of all grades (see section 5.2). Signed informed consent documents will be retained in study files and a copy will be uploaded to the patient's electronic medical record (Epic or site-specific EMR system).

4.2 Protection of patient rights and confidentiality

4.2.1 Patients included in the study will be coded by random Subject Number (SN) which will be used in place of the patients' medical record number (MRN). The key linking the patients' MRN and SN will be stored in a secure, password-protected, HIPPA compliant system per institutional guidelines to which only the investigators and key personnel listed in the protocol have access. All clinical information and QoL survey data will be de-identified before data analysis is conducted. Study data will be entered into REDCap (Research Electronic Data Capture) at OSUWMC. Access to patient medical record number and other unique identifiers will be only given to approved research members. Participating co-sites will not be able to access other sites' participant information; only information from their own site.

4.2.2 All study files, paper or electronic, will be destroyed after 6 years from the final data collection date or by local institutional guideline, whichever is longest.

4.3 Data collection

Patients will have the following baseline and infusion data recorded for up to 12 doses of paclitaxel:

- Demographics: such as age, gender, race, height, weight
- Diagnosis of histologically confirmed breast cancer
- ECOG performance status
- chemotherapy regimen
- dose and route of pre-medications given
- dose and infusion rate of paclitaxel
- dose number of paclitaxel
- infusion hypersensitivity reaction (yes/no)
- if applicable; time of hypersensitivity reaction relative to start of infusion
- if applicable; symptoms, characteristics and course of the infusion hypersensitivity reaction including the use of oxygen and IV fluids
- use of parenteral rescue medication (yes/no)
  - rescue medication(s) and doses administered
- dose number of paclitaxel in which rescue medication was administered
- whether or not the patient was re-challenged with paclitaxel successfully that day and if the infusion was completed
- whether or not the patient had premedications resumed (where applicable) and was re-challenged in the future, and if they experience subsequent infusion HSR

This study will utilize REDCap (Research Electronic Data Capture), a software toolset and workflow methodology for electronic collection and management of clinical and research data, to collect and store data. The Ohio State Research Information Technology Electronic Data Capture will be used as a central location

for data processing and management. REDCap provides a secure, web-based application that provides an intuitive data manipulation interface, custom reporting capabilities, audit trail functionality, real-time data monitoring/querying of participant records, and variations of data exporting/importing. REDCap is hosted by OSUWMC IT in the Ackerman Datacenter (640 Ackerman Road; Room 345).

REDCap instance is located on an internal OSUWMC network. Remote access to this network can be obtained over an encrypted VPN tunnel (AnyConnect). This VPN uses Protocol: DTLS and Cipher: RSA_AES_128_SHA1. Background checks are performed on all staff that are on the network or obtaining VPN access. The study REDCap database will be built and maintained with the assistance of the OSUCCC Recruitment, Intervention & Survey Shared Resource (RISSR).

Due to the fact that data in this Section (4.3) are being shared between institutions, a data use agreement (DUA) will need to be put in place. Since Ohio State University will act as the coordinating center for this project, data from MNCCTN and OSU James Network sites will be sent to Ohio State University. Therefore, a data use agreement will be put into place between OSU and the respective institutions.

4.4 Study Design

This is a randomized, open-label, prospective trial. Up to 110 patients in this double arm study will be enrolled so that 100 can be randomized. Eligible patients initiating paclitaxel-based chemotherapy will be placed on study and observed for their first 2 doses of paclitaxel. Assuming that they did not experience a paclitaxel hypersensitivity reaction with the first 2 doses, they will be randomized at a 1:1 ratio to discontinue pre-medications for all subsequent treatments (experimental arm) or to continue pre-medications for all subsequent treatments (control arm).

4.5 Endpoints

Primary Endpoint: Determine the proportion of patients with grade 2 or greater infusion hypersensitivity reactions that require parenteral rescue medications to treat the reaction after the first 2 doses of paclitaxel with or without continued premedication dosing.

Secondary endpoint: To determine whether an abbreviated pre-medication regimen results in improvement in patient-reported quality of life, as measured by an 11-point numerical analog scale.

Exploratory Endpoints:

- To evaluate the differences in a number of symptoms that might be improved, or worsened, by the hypersensitivity prevention drugs (see appendix II)
- Report the number of patients who, after discontinuing pre-medications, request that the pre-medications be resumed to ameliorate side-effects that the patient thinks have worsened since pre-medications were stopped (i.e. nausea, rash, arthralgia).
- Report weight changes across study periods for both arms of the study
- Report the impact of patient self-reported allergies, prior to starting paclitaxel (2 or more versus 3 or less), on the incidence of infusion HSR and rescue medication usage
- To summarize patient outcomes by race.

4.6 Stratification factors definition and justification

1. Weekly paclitaxel (80 mg/m^2) versus every 2-3-week paclitaxel (175 mg/m2)
2. Planned regimen of HSR premeds: all IV vs all PO or mixed IV/PO

5.0 Treatment Plan

Study calendar

	Up to 14 days prior to registration	Paclitaxel #1	Paclitaxel #2	Time between dose 2 and 3	Paclitaxel #3	Paclitaxel #4	Paclitaxel #5	Paclitaxel #6	Paclitaxel #7	Paclitaxel #8	Paclitaxel #9	Paclitaxel #10	Paclitaxel #11	Paclitaxel #12
Tests & Observations														
Consent	X													
Age, gender, race, Ht, Wt, ECOG	X													
weight	X	X	X		X	X	X	X	X	X	X	X	X	X
Diagnosis of histologically confirmed breast cancer	X													
Serum or urine HCG test if clinical suspicion of pregnancy	X													
Planned paclitaxel chemotherapy regimen	X													
QOL survey prior to each dose of paclitaxel		X	X		X	X	X	X	X	X	X	X	X	X
Randomization 1:1				X										
Premedication regimen - drugs, doses, routes		X	X		X	X	X	X	X	X	X	X	X	X
Paclitaxel dose (mg/m2, and total mg), infusion rate (mL/hr)		X	X		X	X	X	X	X	X	X	X	X	X
Infusion HSR (yes/no)		X	X		X	X	X	X	X	X	X	X	X	X
Time of infusion HSR relative to start of paclitaxel infusion		X	X		X	X	X	X	X	X	X	X	X	X
Use of parenteral rescue medication (yes/no)		X	X		X	X	X	X	X	X	X	X	X	X
Drugs and doses of parenteral medication used		X	X		X	X	X	X	X	X	X	X	X	X
Symptoms, characteristics, and course of the infusion HSR		X	X		X	X	X	X	X	X	X	X	X	X
If infusion HSR, was patient re-challenged with paclitaxel that day (yes/no)		X	X		X	X	X	X	X	X	X	X	X	X
If infusion HSR, and patient was re-challenged with paclitaxel that day, was infusion completed (yes/no)		X	X		X	X	X	X	X	X	X	X	X	X
If previous infusion HSR with dose #3 or beyond and premedications resumed, was paclitaxel re-challenged, and did they experience subsequent infusion HSR (yes/no)					X	X	X	X	X	X	X	X	X	X
QOL - DAILY x 6 days after each dose of paclitaxel		X	X		X	X	X	X	X	X	X	X	X	X

5.1 Premedication treatment plan

5.1.1 Patients will consent to study participation at any time from 14 days prior up to the day of initiating paclitaxel. Consenting patients prior to starting paclitaxel may result in some patients having to come off of the trial before randomization and subsequent planned study intervention, since the majority of infusion HSR's are with the 1st or 2nd paclitaxel exposure. This has been accounted for in the sample size.

5.1.2 All patients will receive dexamethasone 10-20 mg IV/PO, either diphenhydramine 25-50 mg IV/PO or cetirizine 10 mg IV/PO, and either famotidine 20 mg IV/PO, ranitidine 50 mg IV or 150 mg PO, or cimetidine 300 mg IV/PO, all given 30-45 minutes (no sooner than 30 minutes) prior to the start of paclitaxel and for the first 2 doses of paclitaxel. The paclitaxel premedication regimen employed at each participating site (i.e. dosages and routes of administration) will be per standard local practice. Prior to randomization changes to each patient's premedication regimen including the dose or route of administration are discouraged, but allowed per the discretion of the ordering physician, if the patient experienced significant side effects to the aforementioned premedications after their first dose.

5.1.3 Patients will have vital signs obtained prior to the start of each paclitaxel infusion. The chemotherapy nurse will remain bedside or in close proximity to the patient (provided the patient has a mechanism to call for the nurse) for a minimum of the first 15 minutes of each paclitaxel infusion regardless if the patient received premedication or not.

5.1.4 Patients who experience an infusion hypersensitivity reaction (any grade) with the first or second dose of paclitaxel (regardless if rescue medications were administered) will not be eligible for randomization. These patients will not be included when calculating the primary endpoint. These patients will come off study at this time and have no further data collected. Patients who have not experienced an infusion hypersensitivity reaction with the first or second dose of paclitaxel, will be randomized at this time (prior to the 3rd dose) to the experimental arm (all premedications discontinued for future doses) or the standard of care arm (premedications continued for all future paclitaxel doses).

5.1.5 Patients who have received their first 2 doses of paclitaxel without any evidence of infusion HSR and who were randomized to the experimental arm will have all pre-medications - including the steroid (dexamethasone), the H1 antagonist (diphenhydramine or cetirizine) and the H2 antagonist (famotidine/ranitidine/cimetidine) - discontinued prior to all future doses of paclitaxel. These pre-medications would not be resumed prior to any future paclitaxel doses, unless the patient did develop an infusion HSR from paclitaxel, at which point the patient would have reached the primary endpoint.

5.1.6 A minority of patients may choose, or their oncology provider may feel it is clinically necessary, to restart premedications even if they have not experienced an infusion HSR; if this occurs, patients will be considered a protocol discrepancy and not included in the primary analysis. These patients will remain on study and continue with data collection, including QOL, for up to 12 doses of paclitaxel. A sensitivity analysis will be conducted that does include these patients. The number of patients who do decide to restart premeds will be collected, and the reason why they wished to resume. Replacement patients will not be added to the study to account for this scenario.

5.1.7 For patients who are randomized to the standard of care arm, they will continue to receive premedications (dexamethasone, diphenhydramine/cetirizine, famotidine/ranitidine/cimetidine) to try to prevent hypersensitivity reactions prior to all future doses of paclitaxel. In the event the patient is reporting poor tolerability from the dexamethasone or diphenhydramine, and had NOT experienced a paclitaxel infusion hypersensitivity reaction with prior doses of paclitaxel, at the discretion of the local investigator, the dose and/or route of the dexamethasone may be decreased to as low as 6 mg, and the dose and/or route of the diphenhydramine may be decreased to as low as 12.5 mg, but not discontinued. No dose adjustments are permitted for cetirizine or famotidine/ranitidine/cimetidine although the route may be changed. If the patient demanded to have premedications discontinued, or if the oncology provider felt it was clinically necessary, these patients would be considered a protocol discrepancy and not included in the primary analysis. These patients will remain on study and continue with data collection, including QOL, for up to 12 doses of paclitaxel. A sensitivity analysis will be conducted that does include these patients. Replacement patients will not be added to the study to account for this scenario.

5.1.8 If receiving paclitaxel in combination with other chemotherapy, the paclitaxel will be infused first.

5.1.9 The premedication, rescue medication and chemotherapy drugs involved in this protocol are all commercially available and will be billed to appropriate private insurance or government payers.

5.1.10 Patients receiving subsequent doses of paclitaxel after premedications were discontinued who experience a hypersensitivity reaction and require rescue medication administration may have premedications resumed and managed at the discretion of the prescribing physician. These patients will be included when calculating the primary endpoint.

5.1.11 For purposes of the study, all patients will be monitored for hypersensitivity/rescue medication usage and QOL and data recorded for up to 12 doses of paclitaxel (i.e. up to 10 doses after randomization), after which time the patient will come off study as the incidence of hypersensitivity reactions beyond this point would be increasingly rare.

5.2 Rescue medication treatment plan

5.2.1 The use of rescue medication will be defined as the administration of at least 1 parenteral rescue medication including hydrocortisone/methylprednisolone, diphenhydramine, famotidine (or other H2 antagonist) or epinephrine.

5.2.2 If the patient calls, or the nurse administering the paclitaxel observes the patient experiencing symptomatic chest tightness, flushing, abdominal pain, back pain, dyspnea, bronchospasm, hypotension/hypertension, angioedema or any other sign or symptom indicating need for parenteral rescue medication, the paclitaxel infusion will be stopped, and parenteral rescue medications administered and documented in accordance with local institutional policy. The local investigator may follow standard local practice for the treatment of the infusion hypersensitivity reaction in terms of alerts, actions, dosing, and order of rescue medication administration.

5.2.2.1 Provided as a reference is Table 2 “Hypersensitivity Management” based on CTCAE v5.0 or refer to sections 5.2.2.2 through 5.2.2.6 below for a suggested outline of infusion HSR management.

5.2.2.2 If patient displays signs and symptoms of a grade 2 or higher paclitaxel infusion hypersensitivity reaction (requires treatment with parenteral medication), RN to administer hydrocortisone 100 mg IV push over 30 seconds or methylprednisolone 40 mg IV push over 3 minutes. Vital signs as clinically indicated to assess improvement or worsening of the reaction.

5.2.2.3 If symptoms don’t begin to diminish, administer diphenhydramine 50mg IV push over 30 seconds. Additionally, famotidine 20 mg (or other H2 antagonist) may be administered as well.

5.2.2.4 If at any time the patient exhibits severe signs of bronchospasm, angioedema, or airway compromise, administer epinephrine 0.3 mg IM or SQ (0.3 mL of 1:1000 solution), epinephrine may be repeated as needed x 2 for a total dose up to 1 mg.

5.2.2.5 Call the prescribing physician and discuss further management of the reaction, including fluids or oxygen. When signs of hypersensitivity reaction resolve to grade 1 or less, discuss re-initiation of the infusion 50% slower than previous rate.

5.2.2.6 Paclitaxel order sets in the electronic medical record should contain standard parenteral medication orders for the treatment of infusion hypersensitivity reactions as outlined above.

5.2.2.7 The nurse administering the paclitaxel will document the occurrence of any grade hypersensitivity reaction.

6 Statistical Considerations

6.1 Sample size justifications

The true incidence of rescue medication after the 2nd dose is unknown; however, we expect the incidence to be less than 10%, which is the estimated incidence with doses one and two. A 0% to 5% incidence of rescue medication during doses 3 to 10 would be acceptable in patients who have had their premedications discontinued after the second dose.

The primary aim of this randomized prospective trial is to estimate the difference in the rate of grade 2 or greater infusion HSR requiring parenteral treatment (rescue medication) in patients whose premedications are stopped after 2 doses of paclitaxel (experimental arm) to those continue to receive premedications (SoC arm). Patients will be randomized at the 1:1 ratio either to discontinue pre-medications for all subsequent treatments (experimental arm) or to continue pre-medications for all subsequent treatments (standard of care arm). A sample size of 90 patients (45 per arm), based on accrual feasibility, will provide sufficient precision for estimating the difference in grade 2 or higher HSR requiring parenteral treatment between the 2 arms. Table 1 provides the potential confidence interval for various scenarios.

Table 1. 95% Confidence Interval for the Difference in Grade 2+ HSR between Arms with 45 Evaluable Patients per arm

Grade 2+ HSR requiring rescue medication			Confidence Interval	
Discontinue Pre-meds	Continue Pre-meds	Observed difference	Lower and Upper Limits	Half Width
.01	.01	0	(-.04, .04)	.04
.04	.01	.03	(-.03, .09)	.06
.04	.04	0	(-.08, .08)	.08
.07	.04	.03	(-.06, .12)	.09

This sample size is inflated to a total of 100 randomized patients (50 per arm) to account for 10% dropout due to cancellation, ineligibility, and protocol discrepancies post randomization. As we expect 10% of patients will experience infusion HSR in the first 2 cycles of paclitaxel, we anticipate enrolling 110 patients to have 100 patients randomized. The sample size estimate was performed using a normal approximation of the binomial distribution and was calculated using PASS20.

Update: as of May 2023, this trial has consented 75 patients, but we have had 18 consented patients who had an infusion HSR to the 1st or 2nd dose, and therefore they did not make it to randomization (24%). This was higher than the 10% drop-out rate we had initially predicted who not make it to randomization. In order to accommodate the original statistical plan to have 100 randomized (evaluable) patients, our plan is to increase accrual from 110 to 130 patients. Of these 130 patients, we expect about 76% (about 100) to be randomized.

6.2 Accrual time

Within our institution, approximately 3-5 eligible patients would enroll each month. As of May 2023, we have consented 75 patients. With our increased sample size (see section 6.1) and with patients being treated on

protocol and followed for up to 12 doses, we anticipate accrual can be completed in about 36-40 months. Efforts will be made to enroll 20% (20) minority patients to this trial.

6.3 Analysis plan

6.3.1 **Primary endpoint**: The primary analysis will follow the intention-to-treat principle where all patients randomized who were not a cancellation, not ineligible, did not decide to discontinue participation in the trial, or not a major deviation will be analyzed based on the arm to which they were randomized. The proportion of patients having infusion HSR of grade 2 or greater requiring parental treatment (rescue medications) will be estimated along with a 95% confidence interval. The difference in proportions of patients with grade 2 or greater infusion HSR needing rescue medication will be estimated along with a 95% confidence interval using the Z-test of normal approximations of the binomial distributions. As a sensitivity analysis, we will repeat the analysis including patients assigned to the discontinuation arm but decided to restart pre-medications and patients assigned to the continuation arm but demanded to have premedications discontinued as having experienced HSR.

6.3.2 **Secondary endpoint:** Patient-reported quality of life, based on a single item 11-point numerical analog scale at each time point as well as change from baseline will be summarized by median (range) separately by treatment arm. Median (mean) QoL scores will be plotted longitudinally by treatment arm. QoL change from baseline will be compared between arms using the Wilcoxon rank-sum test. Data will be captured prior to each dose of paclitaxel and then every day for 6 days after each dose of paclitaxel (total of 7 days of QOL with each dose of chemotherapy).

6.3.3 **Exploratory endpoints:**

- Each symptom (listed appendix II) will be summarized by median (range) at each time point by treatment arm and the weekly average will be compared between arms using the Wilcoxon rank-sum test.
- The frequency and percentages of patients who, after discontinuing pre-medications, request that the pre-medications be resumed to ameliorate side-effects that the patient thinks have worsened since pre-medications were stopped (i.e. nausea, rash, arthralgia) will be summarized.
- Weight changes over time will be summarized at each time point using mean (standard deviation) and plotted by treatment arm. Weight change from baseline to 10 weeks post-randomization will be compared between arms that receive weekly paclitaxel. using a t-test of two independent samples.
- Frequency of patient self-reported allergies (2 or more versus less) on the incidence of infusion HSR and rescue medication usage will be tabulated.
- The rates of rescue medication by arms will be estimated by race/ethnicity group to explore whether there is a differential effect from stopping hypersensitivity reaction by race/ethnicity.

6.3.4 **Plan for missing data:**

We don't anticipate missing data for the primary endpoint as patients will be required to come to the clinic for their paclitaxel treatment and rescue medication for infusion HSR of grade 2 or greater will be identified during paclitaxel treatment. In the rare event that patients, who have not experienced infusion HSR of grade 2 or greater requiring rescue medication, are lost to follow-up prior to completing their paclitaxel treatment, the reason for their discontinuation will be used to determine whether they should be included in the analysis of the primary endpoint. For all endpoints, the proportion of missing data will be summarized and if the missing data rate is higher than 10%, the mechanism of missing data will be evaluated. If the data appear to be missing at random, mixed model or equivalent likelihood methods will be used to compare the outcomes between treatment arms. If the missing data appear to be missing not at random, multiple imputation along with pattern mixture models will be used to compare outcomes between the treatment arms.

7.0 Measurement / Instrumentation

7.1 Hypersensitivity assessment: Following randomization, patients will be followed for up to 10 doses of paclitaxel. Since the clinical signs and symptoms of paclitaxel infusion HSR may vary and are partially influenced by provider/evaluator assessment, the nurse managing the patient should have standing orders to administer rescue medications as clinically indicated for a grade 2 or greater infusion HSR. For any patient who experiences an infusion hypersensitivity reaction, the local investigator may follow standard local practice for the treatment of the reaction – including stopping the infusion and administering rescue medications for those with grade 2 or greater infusion HSR (e.g., hydrocortisone/methylprednisolone, diphenhydramine, epinephrine, 0.9% NaCl fluids, oxygen). See table 2 below for suggested guidelines for the management of hypersensitivity reaction during paclitaxel infusion:

Table 2: Hypersensitivity Management

Mild symptoms (Grade 1)	Moderate symptoms (Grade 2)	Severe symptoms (> Grade 2)
Mild/transient reaction with no intervention: e.g., transient flushing, sweating, mild rash. May or may not interrupt infusion; observe patient until symptoms have resolved; usually no medical intervention required, resume and complete paclitaxel infusion.	Infusion interruption indicated but responds promptly to symptomatic treatment: e.g., rash, flushing, urticarial, shortness of breath, back, chest, or abdominal discomfort, anxiety, tachycardia. Administer hydrocortisone 100 mg IV, and diphenhydramine 50 mg IV if needed. Resume paclitaxel at a slower rate (25-50% of previous rate) after symptoms resolve to < grade 1. If reaction did not recur, may escalate to original rate. Stop and discontinue paclitaxel that day if symptoms recur after re-challenge.	Not rapidly responsive to symptomatic medication and/or brief interruption of infusion, recurrence of symptoms following initial improvement or hospitalization required or life-threatening symptoms: e.g., sustained hypotension, angioedema, respiratory distress, anaphylaxis. If at any time patient experiences signs of angioedema or airway compromise, administer epinephrine 0.3 mg subcutaneous or intramuscular. Stop and permanently discontinue paclitaxel.

Standard CTCAE criteria V5 Infusion related reaction will be utilized to characterize hypersensitivity reactions during paclitaxel infusions. The criteria for infusion-related reaction are listed in Appendix I and include mild/transient reaction with no intervention required (grade 1), therapy or infusion interruption indicated but responds promptly to symptomatic treatment (grade 2), not rapidly responsive to symptomatic medication and or brief interruption of infusion, recurrence of symptoms following initial improvement or hospitalization required (grade 3) and life threatening consequences requiring urgent intervention (grade 4).

7.2 Overall quality of life (QOL) measurement and symptom experience evaluation: Steroids and H1 antagonist pre-medication regimen can impact QOL in both positive and negative ways. For example, patients on steroids may experience increased positive energy or less pain or, alternatively, suffer from some or many of the negative effect of steroids, which might be cumulative. To better evaluate these effects on QOL, participants will be asked to rate their quality of life prior to each dose of paclitaxel and premedications and for 6 days following each dose of chemotherapy during the follow-up period on a single item numerical analog scale of 0-10. This scale will also be used to evaluate pain, insomnia symptoms and multiple other symptoms (see Appendix II). This is a validated simple measure to assess symptoms and quality of life in cancer patients and will serve as a secondary endpoint.[19] QOL surveys will be administered electronically in REDCap or on paper, per participant preference. Data from paper surveys will be hand-entered into REDCap by approved research staff.

8.0 Adverse Event Reporting

8.1 Adverse events

Potential risks and adverse events that may be reasonably anticipated (i.e., "expected") should be described in the informed consent process/form and do not require prompt reporting to the IRB by Investigators and research staff. The following are examples of events that do not require prompt reporting:

- Adverse events or injuries that are non-serious, expected, or unrelated;
- Deaths not attributed to the research, e.g., from "natural causes," accidents, or underlying disease and the Investigator has ruled out any connection between the study procedures and the participant's death;
- Protocol deviations or violations not involving risks to participants or unlikely to recur;
- Complaints made by research participants not involving risks or complaints that were resolved;
- interim analyses, or other reports, findings, or new information not altering the risk/benefit profile;
- Problems or findings not involving risk (unless the Investigator or research staff member believes the information could affect participants' willingness to continue in the research).

Related internal and external events involving risk, but not meeting the prompt reporting requirements, should be reported in the Buck-IRB system, per OSU Office of Responsible Research Practices guidelines (https://orrp.osu.edu/irb/investigator-guidance/event/).

8.2 Serious adverse events

Reporting of adverse events will follow the OSU Human Research Protection Program Policy and Procedure for Event Reporting. The following events may represent unanticipated problems involving risks to subjects or others and would be promptly reported to the IRB of record:

- Adverse events or injuries that are serious, unexpected, and related;
- Protocol deviations or violations (or other accidental or unintentional changes to the protocol or procedures) involving risks or with the potential to recur;
- Events requiring prompt reporting according to the protocol or sponsor;
- Complaints made by research participants indicating unanticipated risks, or complaints that cannot be resolved by the research staff;

- Unapproved changes made to the research to eliminate an apparent immediate hazard to a research participant
- New information indicating an unexpected change in risks or potential benefits (e.g., literature/scientific reports or other published findings);
- Other problem or finding (e.g., breach of confidentiality, loss of study data or forms, etc.) that an Investigator or research staff member believes could influence the safe conduct of the research.

The events described above should be reported to the IRB of record using the sites approved event reporting mechanism, for example the OSU Buck-IRB system's Event Report function within 10 days of the Investigator's or research staff member's learning of the event. Events resulting in temporary or permanent interruption of study activities by the Investigator or sponsor to avoid potential harm to participants should be reported immediately (within 48 hours) whenever possible.

Injury, poisoning and procedural complications					
CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for <=24 hrs	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					

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