**Title:** Conventional Prophylactic Oral Dexamethasone vs Short-course IV Dexamethasone in Paclitaxel Hypersensitivity

**National Clinical Trial number:** NCT03598426

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LOMA LINDA UNIVERSITY
Cancer Center

**PROTOCOL INFORMATION**
**Title**:
Conventional prophylactic regimen of oral dexamethasone versus short-course intravenous dexamethasone in preventing paclitaxel-related hypersensitivity reactions in gynecologic-oncology patients: A prospective, randomized, open-label study

**Funding Source**: N/A
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**STUDY INFORMATION**
Location of research activity: Loma Linda University Cancer Centers
Expected start/ stop date: July 1st, 2018 to December 31st, 2020
Type of Research: Prospective, randomized, open-label study

**SUBJECT RECRUITMENT AND SCREENING**
- Estimated number of subjects needed for the study: 270
- Age range: Adults over the ages of 18 years of age
- Gender: Females
- Racial ethnic distribution: all races qualify if they meet inclusion criteria
- Target study population: Gynecologic Oncology (GYN Onc) patients receiving treatment at Loma Linda
- Language: English or Spanish speaking patients
- Vulnerable subject info: Vulnerable patients will be excluded
- Recruitment method info: Patients of GYN Onc physicians at Loma Linda starting treatment with paclitaxel containing regimen will be asked if they will be interested in participating.
- Description of consent precautions regarding subject rights and welfare: See attached informed consent
- Pregnancy Status Info: Pregnant patients will be excluded

**INFORMED CONSENT PROCESS**
See attached informed consent

**COMPENSATION**
None

**CONFIDENTIALITY**
All data collected will be absolutely confidential, coded, and made available to only the LLUCC investigators.

**OBJECTIVES**
1. To provide the clinician with an evidence-based guideline in the management of patients with acute hypersensitivity reactions
2. Improve the care of patients experiencing hypersensitivity reactions
3. Prevent fatal complications
4. Improve the understanding of hypersensitivity reactions among health care professionals.
5. To determine the most effective means of preventing paclitaxel hypersensitivity reaction between the following methods:

(1) **Conventional method**: oral dexamethasone (20 mg), taking 12 hours and 6 hours prior to paclitaxel infusion and intravenous administration of $H_1$ and $H_2$ receptor antagonists administered 30 minutes prior to paclitaxel infusion

(2) **Short-course method**: intravenous dexamethasone (20 mg), administered concurrently with H1 and H2 antagonists, 30 minutes prior to paclitaxel infusion

(3) **Combined method**: oral dexamethasone (20 mg), taking 12 hours prior to treatment in addition to intravenous dexamethasone (20 mg), $H_1$ and $H_2$ receptor antagonists administered 30 minutes prior to paclitaxel infusion

## BACKGROUND

Paclitaxel is a crude extract from the bark of the Pacific yew tree *Taxus brevifolia*, a rare, slow-growing plant found in the forests of the Pacific Northwest.[1] Since its discovery in the 1960s, through a National Cancer Institute (NCI) program where thousands of plant extracts were screened in order to find natural products that could treat cancer, many clinical trials have shown that paclitaxel have very potent anti-cancer effects against many tumors. It has therefore become a vital part of many chemotherapeutic regimens used to treat a wide variety of cancer types.[1, 2] As a taxane, paclitaxel exhibits anti-microtubule activity mainly by promoting the assembly of microtubules from tubulin dimers and stabilizing microtubules by preventing depolymerization. The stabilization of microtubules results in the inhibition of the normal reorganization of microtubules vital for mitotic cellular function.[3]

As useful as paclitaxel has been in managing many different types of malignant diseases over the years, one of the potentially serious and dose-limiting toxicities of the drug is the development of hypersensitivity reactions (HSRs) .[4, 5] The immunological mechanism of paclitaxel-associated HSR is not clearly known but there are several literatures that suggests that it might be multifaceted. This is because even though the clinical manifestations of paclitaxel HSR are consistent with a type 1 (immunoglobulin [Ig] E-mediated) HSR, about 77% of all paclitaxel reactions occurred from the first administration of the drug, thereby negating the prior sensitization necessary for the development of an IgE response. Rather, it is postulated that the paclitaxel formulation itself induces mast cell degranulation directly.[4, 5, 6] It can either be caused by paclitaxel (active ingredient) or its vehicle, which consists of 50% 'Cremophor EL' (polyoxyethylated castor oil) and 50% ethanol. The vehicle is necessary because of the aqueous insolubility of paclitaxel. Studies have demonstrated that intravenous administration of Cremophor EL and ethanol can induce histamine release and hypotension; this has therefore caused some to think that it plays a major role in paclitaxel's hypersensitivity reactions. However, basophil histamine release tests in sensitized individuals revealed histamine release only with paclitaxel and not with Cremophor EL or ethanol. In addition, 'Cremophor EL' is not a vehicle for docetaxel (another taxane), yet this drug is also associated with a high incidence of HSRs, suggesting that the taxane moiety is likely the more important factor in causing hypersensitivity reactions.[5,6,7,8]

It has been well documented that up to 42% of patients receiving paclitaxel experience an HSR, with serious (> grade 3) reactions observed in about 2% of patients. [3, 6, 9, 10] Also, up to about 95% of HSRs to the taxanes in general occurs during the first or second doses that is administered, with almost 77% of reactions occurring during the first exposure to the agent.[5, 6, 7, 9] Another observation that is worth noting includes the fact that nearly 80% of patients who will react to a taxane infusion will develop HSR symptoms within the first 10 minutes of drug infusion and many reactions occur with as little as 1mg of the drug being administered.[6, 7, 9]

Due to the very real risk of paclitaxel HSRs, the prescribing information and many other references strongly recommend pre-medicating patients who are to be treated with paclitaxel-containing regimen with a corticosteroid, diphenhydramine, and an H2 antagonist. However, the method and timing of administering these pre-medications (particularly in the case of dexamethasone) have not been standardized .[2,6] One of the oldest and most conventional ways that many clinicians have used in preventing paclitaxel HSR is by prescribing and having the patient take oral dexamethasone (20 mg), 12 hours and 6 hours prior to paclitaxel infusion in addition to intravenous administration of diphenhydramine and a $H_2$ receptor antagonists 30 minutes prior to paclitaxel infusion. There are however some clinicians who prefer using a much simpler approach by pre-medicating with a short-course intravenous infusion of dexamethasone (20 mg), administered concurrently with H1 and H2 antagonists, typically about 30 minutes before the paclitaxel infusion is given to the patient. There are yet some clinicians who use a combination of the two strategies described above on their patients; they have their patients take oral dexamethasone (20 mg) 12 hours prior to treatment, while foregoing the 6 hour dose of oral dexamethasone, but rather adding intravenous dexamethasone to diphenhydramine and a $H_2$ receptor antagonists 30 minutes prior to paclitaxel infusion. [6, 7,11,12] Even though there have been several retrospective clinical trials that have evaluated the effectiveness some of these strategies discussed above, there have not been many well controlled prospective studies evaluating the effectiveness of the conventional prophylactic regimen of oral dexamethasone and short-course intravenous dexamethasone in preventing paclitaxel-related hypersensitivity reactions. To the best of our knowledge, there have not been any prospective or retrospective clinical trials that have compared the differences, if any, of the effectiveness of the three methods described above in preventing paclitaxel HSR.

The goal of this project is to do a prospective study to determine the most effective method in preventing paclitaxel HSR. We will therefore be comparing: 1) Conventional method: oral dexamethasone (20 mg) taken 12 hours and 6 hours prior to paclitaxel infusion in addition to intravenous administration of diphenhydramine and famotidine 30 minutes prior to paclitaxel infusion; 2) Short-course method: intravenous dexamethasone (20 mg) administered concurrently with diphenhydramine and famotidine 30 minutes before the paclitaxel infusion; or 3) Combined method: oral dexamethasone (20 mg) taken 12 hours prior to treatment in addition to intravenous dexamethasone (20mg), diphenhydramine, and famotidine, administered 30 minutes before the paclitaxel infusion.

**STUDY DESIGN**

Single center, prospective, randomized, open-label study.

**INCLUSION CRITERIA**

1. Adult female patients $\geq$ 18 years of age
2. Patients of the Loma Linda University Health (LLUH) gynecologic oncology service
3. Confirmed gynecologic cancer diagnosis of any stage and any gynecologic malignancy
4. Planned treatment with paclitaxel containing regimen either in the adjuvant setting or for palliation
5. Planned treatment with paclitaxel should be for 3 or more cycles given as a weekly or every 3 weeks cycle
6. Paclitaxel should be given as a monotherapy or as part of a combination regimen. If paclitaxel is part of a regimen containing other drugs, the following conditions must be met:
    a. Paclitaxel will be the first chemotherapy regimen to be infused when patient comes in for treatment
    b. Chemotherapy regimen that would be approved for the study are the following:
        i. Paclitaxel/ Carboplatin
        ii. Paclitaxel/Carboplatin/Bevacizumab
        iii. Paclitaxel/Cisplatin/Bevacizumab
        iv. Paclitaxel/Bevacizumab
        v. Paclitaxel/ Ifosfamide
        vi. Paclitaxel/ Pazopanib
7. Patients should have no prior exposure to taxanes (this includes: paclitaxel, docetaxel, and protein-bound paclitaxel)
8. The chemotherapy treatment should be at one of the LLUH Adult Cancer Centers
9. The patient should be an English or Spanish speaking patient

**EXCLUSION CRITERIA**

1. Patients who are not with the gynecologic oncology service
2. Patients who are with the gynecologic oncology service but are not receiving paclitaxel either as a monotherapy or in combination with other regimen
3. Patients who have had prior exposure to taxanes (this includes: paclitaxel, docetaxel, and protein-bound paclitaxel)
4. Patients who are currently on steroid therapy and it is anticipated that therapy will not be discontinued at least a week prior to start of chemotherapy
5. Patients with autoimmune diseases, malignancies, and any other co-morbid condition that might require steroid therapy during chemotherapy. This includes, but not limited to:
    a. Crohn's disease
    b. Immune thrombocytopenia
    c. Lupus nephritis
    d. Multiple sclerosis
    e. Primary brain tumors
    f. Multiple Myeloma
    g. Hodgkin's Lymphoma
6. Patients with uncontrolled diabetes or diabetic or pre-diabetic patients with baseline A1C levels > 8.5
7. Patients who are allergic to diphenhydramine and/or dexamethasone
8. Non-English and Non-Spanish speaking patients

## POWER ANALYSIS

A power analysis was performed in order to estimate the number of patients needed for this trial. Review of prior literature shows that there will be an expected HSR rate of 25%.[3,4] The goal of the study is to be able to detect a reduction in HSR from 25% to 20%. The analysis shows that for a power of 0.8, we will need 90 patients in each of the three arms in order to detect this change in HSR with a $p$ value of 0.05. Thus, we are planning to enroll 270 patients.

## PATIENT SELECTION

The gynecologic oncologist (GYN oncologist) will be primarily responsible for identifying all patients who will be potential subjects in this study. Criteria that the GYN oncologist will use to identify these patients will include but not limited to:

a. Patients who have a documented gynecologic cancer diagnosis
b. About to start treatment with paclitaxel either as a monotherapy or as part of a combination regimen for the first time
c. Meets all the study's criteria for inclusion and have none of the exclusion criteria that is listed above

If a GYN oncologist should determine that a patient could qualify for the study, the physician will follow the following procedures:

1. Counsel and explain to the patient, all the potential risks, benefits, expectations, and any requirements needed to enroll in the study.
2. If the potential subject expresses interest and is willing to participate in the study, the GYN/oncologist will have the patient sign the following:
    a. An informed consent document
    b. HIPAA Authorization for Use of Protected Health Information
    c. California Experimental Subject's Bill of Rights

After all these processes are completed, selected subjects will then be randomized into one of the three arms of the study.

## RANDOMIZATION

A computer randomized list will be developed in advance by Loma Linda University Health Research Consulting Group which will allocate the X participants evenly into 3 different groups. Once a patient has been assessed using inclusion/exclusion criteria and is determined to be a suitable subject for the study, clinicians will refer to the list and administer the corresponding treatment regimen. This will prevent selection bias and produce groups suitable for comparison.

## TREATMENT ARMS

Patients will be randomized into one of these treatment arms:

***Conventional arm:***

In the conventional arm of the study, patients will be given prescriptions with orders to take oral dexamethasone (20 mg), 12 hours and 6 hours prior to paclitaxel infusion. On the day of treatment, patients will receive an intravenous administration of diphenhydramine 50mg and famotidine 20mg 30 minutes prior to paclitaxel infusion.

***Short-course arm:***

In the short-course arm of the study, patients who are randomized into this arm will only receive an intravenous dose of dexamethasone 20 mg, administered concurrently with intravenous diphenhydramine 50mg and famotidine 20mg, administered 30 minutes prior to paclitaxel infusion

***Combined arm:***

Patients who are randomized into the combined arm will be given a prescription to take oral dexamethasone (dexamethasone (20 mg), 12 hours before paclitaxel infusion in addition to receiving intravenous dexamethasone 20 mg, diphenhydramine 50mg and famotidine 20mg 30 minutes prior to paclitaxel infusion.

**STUDY PROTOCOL**

1. The GYN oncologist will enter the study protocol (treatment plan) into the BEACON application after randomization. A pharmacist can help enter the treatment plan into the BEACON application for the GYN oncologist to sign the orders.
2. The pharmacist will review all study protocols entered into the BEACON application and to ensure uniformity and consistency in chemotherapy administration. The pharmacist will follow the following processes in compounding paclitaxel for infusion:
    a. For all first cycles (first time) of chemotherapy administration:
        i. All paclitaxel doses that have been entered into the treatment plan/ study protocol will be diluted in 0.9% sodium chloride (normal saline) to a concentration of 0.7mg/mL.
        ii. Weekly paclitaxel doses, which are normally 80mg /m2 or less, will be infused over one hour and every 3 weeks paclitaxel doses which are normally 135mg/m2 or more will be infused over 3 hours.
    b. For all second cycles of chemotherapy administration:
        i. If patient did not have any reactions during the first cycle of paclitaxel infusion:
            1. All paclitaxel doses that have been entered into the treatment plan/ study protocol will be diluted in 0.9% sodium chloride (normal saline) to a concentration of 0.7mg/mL
            2. Weekly paclitaxel doses, which are normally 80mg /m2 or less, will be infused over one hour and every 3 weeks paclitaxel doses which are normally 135mg/m2 or more will be infused over 3 hours.
        ii. If patient experienced a paclitaxel HSR during the first cycle and it is still continuing treatment:
            1. All paclitaxel doses will be further diluted in 0.9% sodium chloride (normal saline) to a concentration of 0.4mg/mL
            2. Weekly paclitaxel doses, which are normally 80mg /m2 or less, will be infused over two hours and every 3 weeks paclitaxel doses which are normally 135mg/m2 or more will be infused over 4 hours.
3. After the treatment plan is entered and reviewed, the study patient will be scheduled with the pharmacist for a consult. The pharmacist will follow the following process during the patient consultation session:
    a. The pharmacist will thoroughly review the signed informed consent document, HIPAA Authorization for use of Protected Health Information, and California Experimental Subject's Bill of Rights to make sure all documents are signed and dated appropriately.
    b. Based on which treatment group the patient is randomized to, the pharmacist will instruct the patient on how and when he/she should take their dexamethasone prescription prior to treatment. The pharmacist will also review patient's home medications, make sure there are no potential interactions that might be of concern and there are no drugs that patient might be taking that might cause an exclusion from the study.
    c. The pharmacist will also verify patient's preferred outpatient pharmacy (where prescriptions will be picked up by the patient).
    d. After patient consultation and verification of patient's preferred pharmacy, and if applicable, the pharmacist will call or fax in any pertinent prescriptions that the patient will need to take prior to starting treatment.

On the day prior to treatment, the investigator or study coordinator will follow the following processes to prepare patients for treatment:

1. Review patient's chart and treatment schedule to verify what time patient is scheduled for treatment
2. Call the patients scheduled for treatment to confirm appointment time
3. If applicable, verify that all patients who are scheduled for treatment picked up their prescriptions from the pharmacy.
4. They will also verify that patients know exactly what time to take their prescription dexamethasone and what time they are scheduled for their chemotherapy treatment.

On the day of treatment the following processes will be followed:

1. The investigator or study coordinator will meet with the patient prior to the paclitaxel infusion and have the patient fill out a questionnaire with the main purpose of determining if they have been compliant with the directions given to them about paclitaxel pre-medication with dexamethasone (if applicable) prior to treatment (see **appendix A** for questionnaire).

**Protocol Appendix A**

**Patient Questionnaire**

1. **Were you given a prescription for dexamethasone (decadron) oral to take at home prior to chemotherapy?**
   a. **Yes**
   b. **No**
2. **Only if you answered yes to question #1: what dose of dexamethasone were you given?**
   a. **20mg**
   b. **12mg**
   c. **Other dose (please specify):**
   d. **I was not prescribed dexamethasone**
3. **Only if you answered yes to question #1: when were you instructed to take your dose of dexamethasone?**
   a. **12 hours before and 6 hours before chemotherapy**
   b. **12 hours before chemotherapy only**
   c. **Other instructions (please specify):**
   d. **I was not prescribed dexamethasone**
4. **Did you take your dexamethasone prescription as prescribed?**
   a. **Yes**
   b. **No**
   c. **I was not prescribed dexamethasone**
5. **If your answer to question #4 was Yes, what time(s) did you take your dexamethasone?**
6. **If your answer to question #4 was No, please specify why you did not take dexamethasone as prescribed. If you were not prescribed dexamethasone, please leave blank.**

2. Prior to start of infusion, the infusion registered nurse (RN) will consult with the study research coordinator to verify that the patient in question is in fact a study patient and enrolled on this study
3. The infusion RN will also verify that all pertinent consent forms including informed consents, HIPAA Authorization for Use of Protected Health Information, and others have been signed
4. The infusion RN will follow standard policies and procedures to administer patient's chemotherapy
   a. This will include adhering to the institution's HSR protocol and following all policies and procedures if patient reacts to paclitaxel administration ***(see appendix B)***.
5. If a paclitaxel HSR occurs during treatment, in addition to adhering to the institution's HSR protocol, RN will be expected to document all occurrences per institutional policies and also use the smart phrase in EPIC to document occurrences and interventions in the multidisciplinary progress notes (***see appendix C***).

6.

a. This step is necessary to ensure that all vital data are captured for analysis

**Protocol Appendix C**

**RN Progress Note (SMART PHRASE)**

1. **Patient diagnosis:** ***
2. **Chemotherapy regimen patient received:** ***
3. **Time paclitaxel infusion started:** ***
4. **Was a reaction noted: Y/N*****
    a. **If yes, what grade reaction did the patient develop:** ***
        i. **What time was the reaction noted?** ***
    b. **What interventions were made? (Circle all that apply)**
        i. **Stop infusion** Y/N***
        ii. **Oxygen to keep O2 sats > 90%** Y/N***
        iii. **Respiratory therapist paged** Y/N***
        iv. **Call a code (7777)** Y/N***
        v. **Elevate legs** Y/N***
        vi. **Admit to hospital** Y/N***
        vii. **NaCl bolus to maintain BP** Y/N***
    c. **Were any medications given?** Y/N***
        i. **If medications were given, what medication(s) were given? ( circle all that apply)**
            1. **Diphenhydramine IV** Y/N***
            2. **Diphenhydramine PO** Y/N***
            3. **Hydrocortisone IV** Y/N***
            4. **Famotidine IV** Y/N***
            5. **Epinephrine** Y/N***
    d. **Was a physician notified?** Y/N***
        i. **If yes, what time was a physician notified?** ***

7. The GYN/oncologist will primarily be responsible for assigning grades of all paclitaxel HSR that occurs during treatment. The grades will be assigned based on symptoms documented by the RN and in accordance with the NCI Common Toxicity Criteria for Adverse Effects:

| **NCI Common Toxicity Criteria for Adverse Effects** | |
|---|---|
| **Grade** | **Hypersensitivity Reaction** |
| **1** | • **Transient flushing**<br>• **Rash**<br>• **Drug fever** |
| **2** | • **Rash**<br>• **Flushing**<br>• **Urticaria**<br>• **Dyspnea**<br>• **Drug fever above 100.4F** |
| **3** | • **Bronchospasm with or without urticarial**<br>• **Edema**<br>• **Angioedema**<br>• **Hypotension** |
| **4** | • **Anaphylaxis** |
| **5** | • **Death** |

8. After treatment is completed for that cycle, the investigator will put in all documented data in an excel spreadsheet. Data that will be collected will include but not limited to the following:

**1. Coded patient identifier**
**2. Patient diagnosis**
**3. Date patient was randomized into study**
**4. Study arm**
**5. Oral dexamethasone prescribed (Y/N)**
**6. Time patient took oral dex night prior to chemo (if applicable)**
**7. Time patient took oral dex on day of treatment (if applicable)**
**8. Chemotherapy regimen**
**9. Chemotherapy cycle number**
**10. Date of treatment**
**11. What dose of paclitaxel is patient receiving**
**12. Time pre-medication (intravenous diphenhydramine) was started**
**13. Time pre-medication (intravenous dexamethasone) was started**
**14. Time pre-medication (intravenous acetaminophen) was started**
**15. Time paclitaxel infusion started**
**16. Time paclitaxel infusion ended**
**17. Did HSR occur (Y/N)**
**18. If HSR occurred, what time was it first noticed/ documented**
**19. What grade of HSR did patient have**
**20. What interventions were made by the RN**
**21. What medications were administered per HSR protocol**
**22. What time did patient recover from HSR**
**23. What time was paclitaxel resumed**
**24. Was paclitaxel discontinued after the HSR (Y/N)**

## OUTCOME VARIABLES

**Primary outcomes**:

1. The treatment group that had the least incidence of any-grade-paclitaxel-HSR in the first cycle of chemotherapy treatment
2. The treatment group that had the least incidence of any-grade-paclitaxel-HSR in the second cycle of chemotherapy treatment
3. The treatment group that had the least incidence of grade 3 or more paclitaxel-HSR in the first cycle of chemotherapy treatment
4. The treatment group that had the least incidence of grade 3 or more paclitaxel-HSR in the second cycle of chemotherapy treatment

**Secondary outcomes:**

1. The treatment group that had the least incidence of any-grade-paclitaxel-HSR in the first and second cycles of chemotherapy treatment
2. The treatment group that had the least incidence of grade 3 or more paclitaxel-HSR in the first and second cycles of chemotherapy treatment

## STATISTICAL CONSIDERATION

SAS version 9.4 will be used for all analyses. To determine whether there is an association between incidence of hypersensitivity as a dichotomous outcome and treatment regimen (consisting of 3 groups) as the main predictor, a simple test of proportions will be conducted. To obtain more accurate estimates and potentially increase the power of the analysis[13], a log-binomial regression model will be developed to estimate adjusted risk ratios (RR) and 95% confidence intervals. If convergence difficulties arise, a Poisson regression with robust variances will be used to estimate RRs[14]. For the secondary outcome of hypersensitivity grades 1 – 5, ordinal regression will be used.

**References**


1. Rowinski EK and Donehower RC. Paclitaxel (Taxol). *N Engl J Med* 1995; 332:1004-1014. DOI: 10.1056/NEJM199504133321507
2. Mestrovic, T. What is paclitaxel. News Medical: Life Sciences & Medicine. http://www.news-medical.net/health/What-is-Paclitaxel.aspx. Published 2014, Accessed [June 3, 2017]
3. Taxol (R) [package insert]. Princeton, New Jersey: Bristol-Myer's Squibb Company; 2011
4. Kwon JS, Elit L, Finn M, Hirte H, et al. A Comparison of Two Prophylactic Regimens for Hypersensitivity Reactions to Paclitaxel. *Gynecologic Oncology,* 2002; 84: 420–425. doi:10.1006/gyno.2001.6546
5. Markman M, Kennedy A, Webster K, Kulp B, et al. Paclitaxel-Associated Hypersensitivity Reactions: Experience of the Gynecologic Oncology Program of the Cleveland Clinic Cancer Center. *Journal of Clinical Oncology*, 2000; 18(1):102-105
6. Zanotti KM & Markman M. Prevention and Management of Antineoplastic-Induced Hypersensitivity Reactions. *Drug Safety*, 2001;24(10):767-779. DOI: 10.2165/00002018-200124100-00005
7. Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, Baker, J Echo, et al. Hypersensitivity Reactions From Taxol. *Journal of Clinical Oncology*, 1990; 8(7):1263-1268. http://jco.ascopubs.org/content/8/7/1263.long. Accessed July 19, 2016
8. Taxotere (R) [Package Insert]. Princeton, New Jersey: Ebewe Pharma; 2012
9. Verweij J, Clavel M, Chevalier B. Paclitaxel (Taxol) and docetaxel (Taxotere): not simply two of a kind. *Ann Oncol*, 1994; 5: 495–505
10. Eisenhauer EA, ten Bokkel Huinink WW, Swenerton KD, et al. European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol,* 1994; 12: 2654–66
11. Bookman MA, Kloth DD, Kover PE, Smolinski S, Ozols RF. Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. 1997 Jun;8(6):611-4.
12. Kintzel PE. Prophylaxis of paclitaxel hypersensitivity reactions. *Ann Pharmacother,* 2001;35:1114-7.
13. Kahan, B. C., Jairath, V., Doré, C. J., & Morris, T. P. (2014). The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials*, *15*(1), 139.
14. Donna Spiegelman, Ellen Hertzmark; Easy SAS Calculations for Risk or Prevalence Ratios and Differences, *American Journal of Epidemiology*, Volume 162, Issue 3, 1 August 2005, Pages 199–200, https://doi.org/10.1093/aje/kwi188

# Hypersensitivity Reactions Management

# Protocol

# Cancer Center

# Loma Linda University Medical Center

## Hypersensitivity Reactions Management

## Protocol – Appendix B

**Introduction:**

Acute reactions to chemotherapy do not occur frequently. There are a few selected drugs that are associated with severe reactions. Medications associated with hypersensitivity reactions include cytotoxic agents such as the taxanes, platinum based com pounds and monoclonal antibodies such as rituximab, alemtuzumab, trastuzumab, bevacizumab, cetuximab and panitumumab.

For the most part reactions occur after the first or second infusion of these medications and may vary in severity from a mild reaction to a life threatening event. These reactions may occur during the administration or several hours after the infusion. Risk factors for hypersensitivity reactions include: the administration of an agent known to cause hypersensitivity reactions, previous history of allergic reactions, previous exposure to the agent and failure to administer appropriate premedication.

Small percentage of patients present with bronchospasm, urticaria, hypotension and / or cardiac arrest. These reactions are unpredictable and may occur despite premedication. These events can be fatal without the prompt recognition and intervention of skilled clinicians. It is important that clinicians are prepared to recognize symptom s of hypersensitivity and have protocols in place to prevent and manage these reactions.

**Objectives:**

1. Provide the clinician with an evidence-based guideline in the management of patients with acute hypersensitivity reactions.
2. Improve the care of patients experiencing hypersensitivity reactions.
3. Prevent fatal complications.
4 Improve the understanding of hypersensitivity reactions among health care professionals.

**Definitions:**

Hypersensitivity reaction (HSR): allergic- type reaction to biological agent, chemotherapy or metal- based material. It occurs when the immune system identifies the agent as an antigen; initiating a histamine release reaction.

Anaphylactic reaction: involves the sudden release of mast cells and basophil mediators and is mediated by the fixation of Immunoglobulin E (IgE) to mast cells.

Anaphylactoid: reaction not mediated by IgE, resulting in a partial hypersensitivity. This reaction is less life threatening.

**Population:**

This protocol will apply to all medical staff and registered nursing staff working with adult patients (age 18 and over) within the Cancer Center at Loma Linda Medical Center, after completion of a Hypersensitivity Reactions Management training session.

In addition, Pharmacy will ensure that drugs needed for the implementation of this protocol are available in the Accudose machine.

Treatment Guidelines for this protocol are based on:

1. The ONS guidelines for the management of hypersensitivity reactions and anaphylaxis. http://www.ons.org/

2. The American Academy of Allergy, Asthma and Immunology and the American College of Allergy, Asthma and Immunology: The diagnosis and management of anaphylaxis and updated practice parameter.

**Criteria for Intervention**

Patients receiving therapy that experience the following symptoms determined by the nurse to be caused by the treatment:

A sense of uneasiness and or agitation, chest tightness accompanied by shortness of breath with or without wheezing, hives, itching, hypotension, hypertension, tachycardia or bradycardia. Bronchospasms, facial or periorbital edema; dizziness, lightheadedness; change in mental status; abdominal cramping, nausea, vomiting, diarrhea. These reactions may occur within minutes to hours after the start of the infusion. Signs and symptoms highly suggestive of anaphylaxis include: urticaria, cough, wheezing, and throat tightness.

**Management**

1. Stop infusion
2. Stay with the patient, have another staff member notify MD or NP.
3. Monitor vital signs and record.
4. Place patient in the supine position (if tolerated) to maintain blood flow to vital organs.
5. Oxygen to keep oxygen saturations above 90%
6. Assess airway, breathing, circulation and mental status
7. For severe allergic reactions accompanied by hypotension and bronchospasm call code blue at 7777
8. Maintain IV access.
9. See treatment algorithm in Appendix 3
10. Normal saline bolus 1-2 liters intravenous if hypotensive.
11. Give the following as indicated:
    - Diphenhydramine 25-50 mg IV
    - Famotidine 20 mg IV
    - Hydrocortisone 100 mg IV
    - Epinephrine 1: 1000 (1 mg /mL) 0.5 mg IM (preferred) in the anterolateral thigh. Can repeat every 5 minutes as needed. Epinephrine should be administered IM to patients with difficulty breathing, inspiratory stridor, wheeze, cyanosis, tachycardia. Epinephrine is available in 2 strengths: for anaphylaxis, epinephrine is used in a dilution of 1: 1000 IM, and for cardiac arrest: the dilution is 1: 10000 IV.
    - If wheezing is present and not responding to epinephrine Call Respiratory Therapy to administer Med Neb with 0.5 mL of 0.5% albuterol.
12. Provide emotional support to the patient and family.
13. Document all treatments and the patient's response in the medical record.
14. Symptoms of anaphylaxis may recur hours after initial intervention. Patients that have experienced a severe reaction should be hospitalized and monitored closely for 24 hours.
15. Document patient and family education.

**Grading of HSRs** **APPENDIX 1**

(NCI Common Toxicity Criteria for Adverse Events)

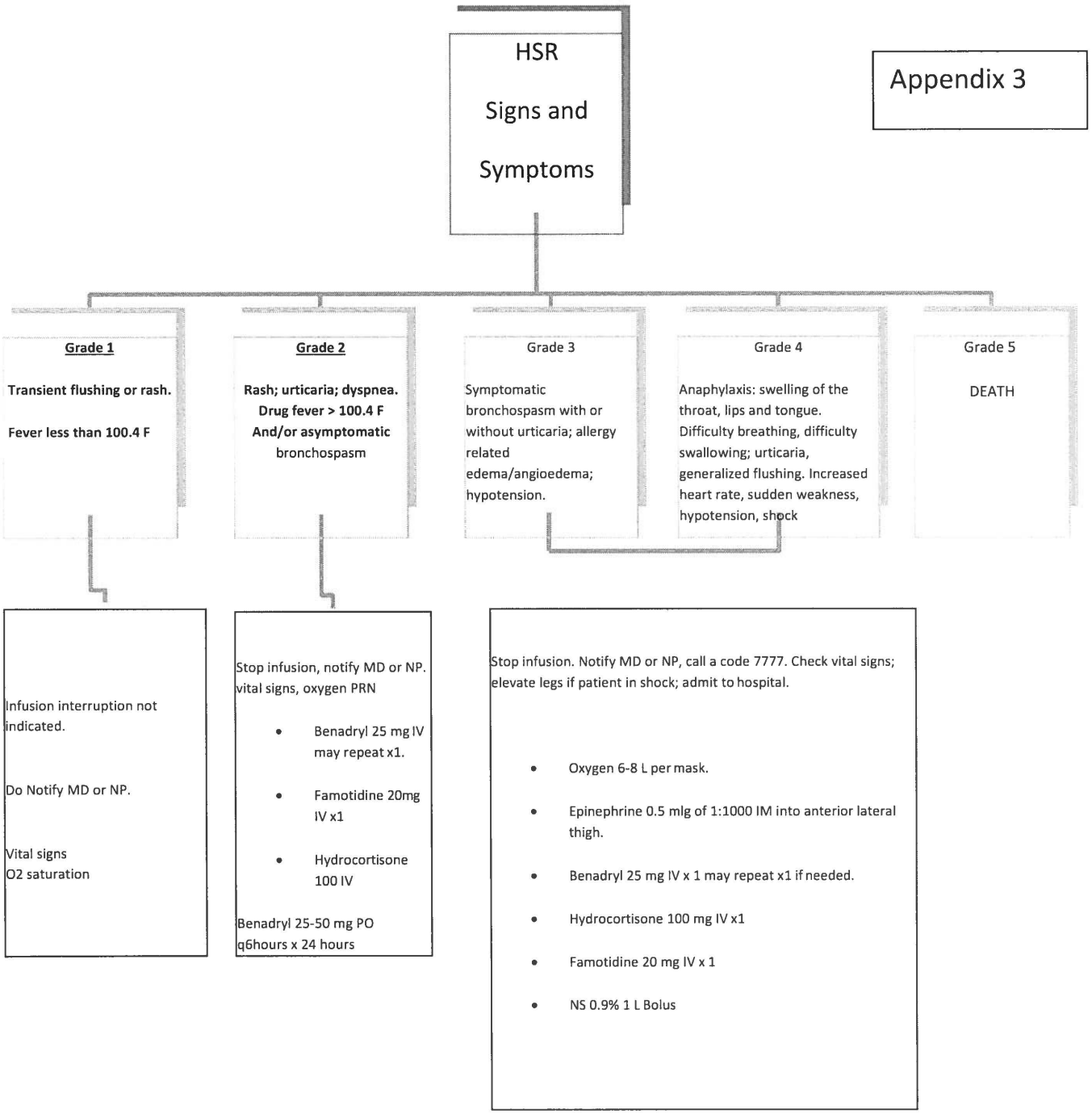
| Grade | Hypersensitivity Reaction | Management |
|---|---|---|
| 1 | Transient flushing or rash, drug fever | Mild reaction. Infusion interruption is not indicated. |
| 2 | Rash, flushing, urticaria, dyspnea, drug fever above 100.4 F | Requires infusion interruption. Responds promptly to symptomatic treatment such as antihistamines, NSAIDs, narcotics, IV fluids. Prophylactic medication is indicated for 24 hours. |
| 3 | Bronchospasm with or without urticaria, edema, angioedema, hypotension. | Not responsive to symptomatic medication or IV interruption of infusion. Parenteral medications are indicated. Hospitalization is indicated if renal impairment or pulmonary infiltrates. |
| 4 | Anaphylaxis | Life threatening; vasopressor or ventilator support is indicated. |
| 5 | Death | Death |

**APPENDIX 2**

**Drugs Associated with Hypersensitivity Reactions**

| Drug | Onset | Incidence |
|---|---|---|
| Alemtuzumab | not defined | 26-96% severe 9-16% |
| Asparaginase | 30-60 minutes | Severe 3-32% |
| Bleomycin | ½-6hours after 1$^{st}$ or 2$^{nd}$ dose | 1% |
| Cetuximab | Not defined | Severe 3% |
| Carboplatin | Usually immediately after the start of infusion; however there are reports of delayed reactions | 2-30% |
| Docetaxel | A few minutes after the start of the infusion | 21% severe |
| Etoposide | Either during infusion or up to several hours | 1-3% |
| Oxaliplatin | Within 30 minutes, but may occur any time during the infusion | Severe 3% |
| Paclitaxel | 53% within 2-3 minutes of infusion and 78% occur within 10 minutes. | 41% severe |
| Rituximab | 1-2 hours after start of infusion | Up to 80% |
| Trastuzumab | During infusion | 30-39% |
| Tositomomab | Not defined | Severe 6% |

Appendix 3


HSR
Signs and
Symptoms
Grade 1
Transient flushing or rash.
Fever less than 100.4 F
Grade 2
Rash; urticaria; dyspnea.
Drug fever > 100.4 F
And/or asymptomatic
bronchospasm
Grade 3
Symptomatic bronchospasm with or without urticaria; allergy related edema/angioedema; hypotension.
Grade 4
Anaphylaxis: swelling of the throat, lips and tongue. Difficulty breathing, difficulty swallowing; urticaria, generalized flushing. Increased heart rate, sudden weakness, hypotension, shock
Grade 5
DEATH
Infusion interruption not indicated.
Do Notify MD or NP.
Vital signs
O2 saturation
Stop infusion, notify MD or NP. vital signs, oxygen PRN
Benadryl 25 mg IV may repeat x1.
Famotidine 20mg IV x1
Hydrocortisone 100 IV
Benadryl 25-50 mg PO q6hours x 24 hours
Stop infusion. Notify MD or NP, call a code 7777. Check vital signs; elevate legs if patient in shock; admit to hospital.
Oxygen 6-8 L per mask.
Epinephrine 0.5 mlg of 1:1000 IM into anterior lateral thigh.
Benadryl 25 mg IV x 1 may repeat x1 if needed.
Hydrocortisone 100 mg IV x1
Famotidine 20 mg IV x 1
NS 0.9% 1 L Bolus

**APPENDIX 4**

**Emergency Drugs:**

| | |
|---|---|
| Epinephrine | • Administer IM ( preferred) or IV in anaphylaxis or allergic reaction<br>• Potent adrenoreceptor agonist<br>• Vasoconstrictor<br>• Increases heart rate and contraction force, thus increasing cardiac output and blood pressure. |
| Diphenhydramine | • H1 blocker<br>• It is given to block the effects of histamine |
| Famotidine | • H2 blocker<br>• Given to block the effects of histamine |
| Hydrocortisone | • Used to prevent delayed recurrence of symptoms<br>• Some reactions can cause symptoms up to 24-30 hours after original episode.<br>• Decreases bronchoconstriction and improves cardiac function. |

**REFERENCES**


1. Chung H. C. ( 2008) Managing premedications and the risk for reactions to infusional monoclonal antibody therapy. *The Oncologist: Symptom Management and Supportive Care* 2008; 13: 725-732.

2. Hallquist, P., ( 2008). Hypersensitivity reactions: A call to action workshop. *Institute for Medical Education and Research.* Retrieved from www. imeronline.com

3. Heinz, J . ( 2007) Management and preparedness for infusion and hypersensitivity reactions. *The Oncologist. 12 : 601- 609.*

4. LaCasce, A, et al ( 2009) Infusion reactions to therapeutic monoclonal antibodies used for cancer therapy. www.uptodate.com

5. Lieberman, P. et al ( 2005) The diagnosis and management of anaphylaxis: an updated practice parameter. Joint Task Force representing the American Academy of Allergy and Asthma and Immunology; the American College of Allergy, Asthma and Immunology.

6. Mario L de Lemos, M. ( 2006). Acute reactions to chemotherapeutic agents. *Journal of Oncology Pharmacy*. 12: 127-129.

7. ONS: Hypersensitivity and anaphylaxis, in Polovich, M, White, JM, Kelleher LO: ONS Chemotherapy and Biotherapy Guidelines: recommendations for practice, 32nd ed. pp 83- 87. Pittsburgh, ONS, 2009.