

Review Article: Mechanisms and Efficacy of Using Diphenhydramine as a Chemotherapy Premedication

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Abstract

The use of chemotherapeutic agents can cause side effects that have a negative impact on the patient's quality of life and have the potential to cause unexpected reactions. This reaction is known as a hypersensitivity reaction where. This reaction occurs at therapeutic doses that resemble allergic reaction. The effects of these reactions can range from mild to life-threatening. The use of diphenhydramine as a chemotherapy premedication has been widely studied for its effectiveness in reducing the risk of hypersensitivity and toxicity from the use of chemotherapeutic agents. Therefore, this review article aims to provide an understanding of the importance of the use of premedication, as prevention of hypersensitivity reactions and reduce the potential for toxicity from the use of chemotherapeutic agents. The method used in this literature study is to identify and review various research articles through the MeSH PubMed database, ScienceDirect with the keywords "Diphenhydramine", "Prevention", "Premedication", "Hypersensitivity Reaction" "Toxicity" and "Chemotherapy" as relevant references. An analysis was conducted on relevant research articles related to the mechanism and efficacy of diphenhydramine in the use of chemotherapy. The research article that forms the basis for writing this literature study, as a whole, shows that the use of diphenhydramine as an anti-histamine is one of the effective prophylaxis that can be used before the use of chemotherapy agents to minimize the occurrence of unwanted hypersensitivity and toxicity effects.

Keywords: Diphenhydramine, Hypersensitivity, Toxicity, Chemotherapeutic Agent.

INTRODUCTION

Cancer incidence is expected to increase from 17 million to 26 million between 2018 and 2040¹. The increase in cancer cases, perhaps benefiting from the use of chemotherapy, has led to rapid development of chemotherapeutic agent design¹⁻³. However, chemotherapeutic agents in cancer patients can potentially cause fatal hypersensitivity reactions⁴. A hypersensitivity reaction is defined as an unexpected reaction to chemotherapy use⁵⁻⁷. The risk of hypersensitivity reactions will increase with the cycle of therapy and the type of chemotherapy used. Symptoms of hypersensitivity from the use of chemotherapeutic agents can include difficulty breathing, redness, hypotension, nausea and tachycardia⁶. Hypersensitivity reactions can occur within seconds or minutes after drug administration which is characterized by an anaphylactic reaction⁵. The use of chemotherapeutic agents that cause hypersensitivity reactions can still be used by carrying out prevention and treatment methods⁸. One method of preventing and treating hypersensitivity reactions due to the use of antineoplastics is the use of antihistamines⁹. Antihistamines are considered to be able to suppress hypersensitivity reactions caused by high levels of histamine in cancer patients by reducing the immunotherapy response so that they can be used as adjuvant agents¹⁰. Diphenhydramine is a first-generation histamine H1 receptor antagonist, which is commonly used to reverse the effects of histamine on capillaries, thereby reducing the symptoms of allergic reactions¹¹. Diphenhydramine is the first generation of injectable antihistamines with a rapid onset of action¹². The use of diphenhydramine as an antihistamine is one of the premedications that have been empirically introduced to reduce reactions related to chemotherapy infusions¹³. Therefore, this literature study aims to provide a review regarding antihistamines, especially diphenhydramine as a preventive option for the prevention of HSRs in patients receiving chemotherapy therapy, and to determine the mechanism and efficacy of diphenhydramine in HSRs against neoplastic agents.

Method

The method used in this review article uses a systematic review to identify studies related to the mechanism and efficacy of diphenhydramine as a chemotherapy premedication. We identified various research articles through the MeSH PubMed database, ScienceDirect with the keywords "Diphenhydramine", "Prevention", "Premedication", "Hypersensitivity Reaction" "Toxicity" and "Chemotherapy" as relevant references. We grouped studies related to inclusion related to relevant articles and excluded duplicate articles, review articles, duplicated data and articles that were not relevant to the use of diphenhydramine, chemotherapeutic agents, or their effect on the condition of HSRs, IR or toxic effects caused by

chemotherapeutic agents. We included 15 relevant articles and analyzed the mechanism and efficacy of diphenhydramine on chemotherapy which was used as the main source of writing in this review article.

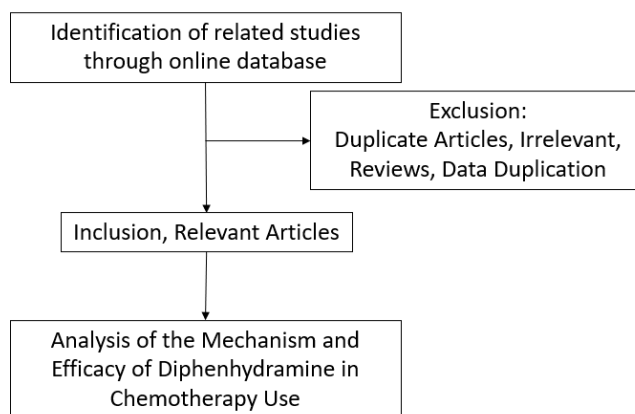


Figure 1. The flow of the Review Article Method used

Overview

CHEMOTHERAPY

Chemotherapy is a treatment action to kill cancer cells. Chemotherapy has benefits including relieving symptoms, controlling spread, and healing¹⁴. The use of chemotherapy aims to inhibit cell proliferation and tumor multiplication, thereby avoiding invasion and metastasis¹⁵. Chemotherapy drugs can be classified, including^{16,17}

1. Alkylating Agent, has a reactive group attached to DNA or RNA, causing interference in the synthesis of DNA, RNA, or protein. e.g: Cisplatin, busulfan.
2. Antimetabolites, are structural analogues of naturally occurring molecules required for the synthesis of DNA and RNA. When replaced with other substances it will interfere with the synthesis of DNA and RNA. e.g gemcitabine, fluorouracil.
3. Antimicrobial Agents (Mitotic Inhibitors), inhibit the process of mitotic cells by interfering with the formation or function of microtubules. e.g : Paclitaxel, Vincristine.
4. Topoisomerase Inhibitors (I and II), causes DNA strand breakage by interfering with the function of the enzyme topoisomerase, which regulates the 3-D structure of DNA. e.g: Topoisomerase I (irinotecan), Topoisomerase II (Etoposide, Doxorubicin).
5. Hormonal Therapy, works by manipulating the endocrine system through the administration of specific exogenous or external hormones, especially steroid hormones. e.g : Prednisone, Tamoxifen.
6. Antibiotics, work by inhibiting the synthesis of RNA and DNA. e.g: Actinomycin D, Bleomycin, Daunomycin.

Common side effects in individuals undergoing chemotherapy are fatigue, loss of appetite, nausea, vomiting, hair loss, infection, anemia, bruising and bleeding, canker sores, skin and nail problems^{15,18,19}. In addition, another potential effect that has been widely reported from the use of chemotherapy is hypersensitivity reactions^{5,9,15}.

All chemotherapeutic agents can induce hypersensitivity reactions (HSR), with different incidences depending on the causative drug⁴. The chemotherapeutic agents most commonly associated with HSR reactions include taxane (8-50%), L-asparaginase (6-43%), platinum (10-27%), doxorubicin, procarbazine, etoposide (1-3%), teniposide (5%), and cytarabine^{4,20-22}.

HYPERSENSITIVITY REACTIONS (HSRS)

A hypersensitivity reaction is an overreaction of the immune system to an antigen that does not normally trigger an immune response²³. The reactions that arise involve the immune system, but some are allergic and are mediated by immunoglobulin E (IgE)²⁴. Adverse drug reactions, including drug hypersensitivity reactions, can be immunologically or non-immunologically mediated²³. HSRs are largely mediated by IgE, IgM, and IgG antibodies²⁵. HSRs involving IgE antibodies are also known as direct reactions into Type I HSRs²⁵⁻²⁷.

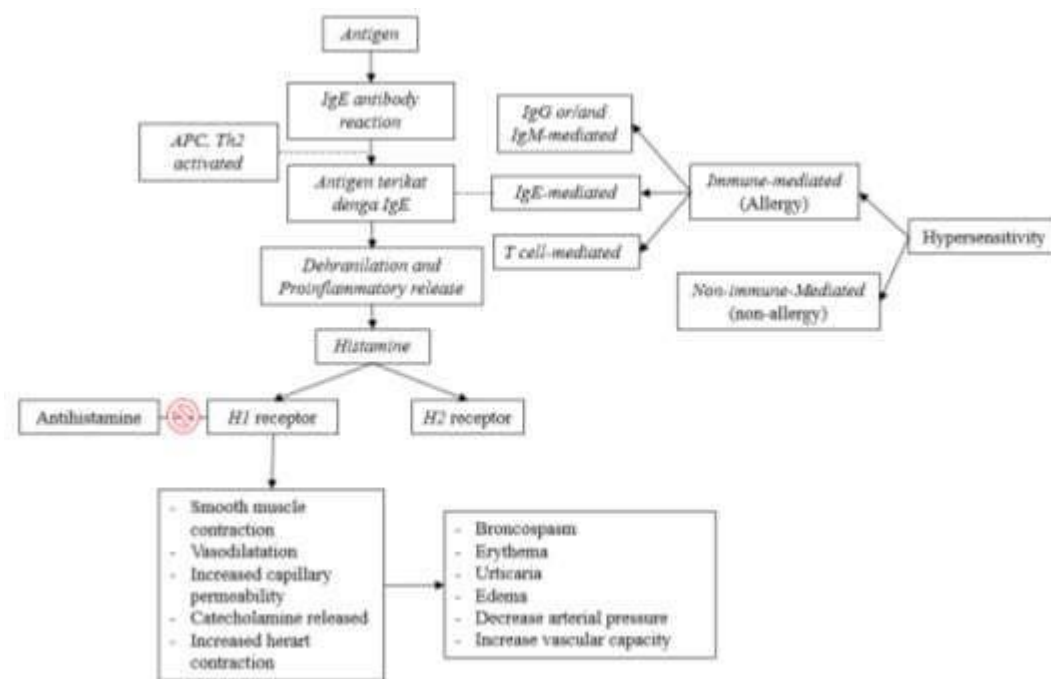


Figure 2. Mechanism of Type I . Hypersensitivity Reaction

The classification of drug-induced HSRs depends on the mediator of clinical presentation, cause and timing. Gell and Coombs classified HSRs into four types as shown in table 1²⁸.

Table 1. Classification of Hypersensitivity (Gell and Coombs 1968; Dispenza 2019; Baldo and Pham 2013).

	Hypersensitivity Classification			
	Type I	Type II	Type III	Type IV
Mediator	IgE (<i>Immediate</i>)	Cytotoxic reaction (IgG/IgM) (<i>Antibody-Mediated</i>)	Complex Immune reaction (IgG and IgM) (<i>Immune complex Mediated</i>)	T cells (<i>Cell-Mediated</i>).
Mechanism	Th-2 and its mediators stimulate IgE production. When a specific allergen binds to IgE, IgE cross-linking induces mast cell degranulation, thereby inducing inflammatory cells.	IgG/IgM that binds to the antigen, will cause a cytotoxic response in the host cell itself.	IgG and IgM that bind to antigens will form immune complexes that are stored in tissues and activate complement that causes organ damage.	Th1 cells produce cytokines that will activate macrophages and cytokine T cells that can cause tissue damage.
Clinical Presentation	Allergic reactions include redness, itching, swelling, asthma, anaphylaxis, bronchoconstriction, and vascular permeability.	Immune thrombocytopenia, anemia, autoimmune hemolytic and autoimmune neutropenia.	Systemic lupus erythematosus, rheumatoid arthritis, vasculitis.	Contact Dermatitis, Type 1 DM, persistent asthma, allergic rhinitis.

Cause	Food, Drugs or Insects	Drugs, maternal IgG that crosses the placenta, IgG and IgM that bind to antigens in transfused blood	Autoimmune	Exposure to toxic compounds
Time	0-6 hours after exposure.	2-24 hours after exposure.	24 hours to 2 days after exposure.	About 24 hours after exposure.

Mediators that play a role in the response of HSRs include histamine. Histamine-mediated physiological and pharmacological effects can be mediated through four receptors, H1, H2, H3, and H4²⁶. Mast cells are the main producers of histamine in the body. H1 is expressed in many cells, including mast cells involved in type 1 HSRs³⁰. Stimulation of the H1 receptor causes pathophysiological effects resulting in an immediate allergic reaction in the form of redness, itching, swelling, asthma, anaphylaxis, bronchoconstriction, and vascular permeability (see Figure 1)²⁶.

The potential for hypersensitivity reactions resulting from the use of chemotherapeutic agents can occur suddenly, and can worsen rapidly^{9,31,32}. Management related to the treatment of HSRs is considered very important, to avoid unwanted fatal effects (see Figure 2).

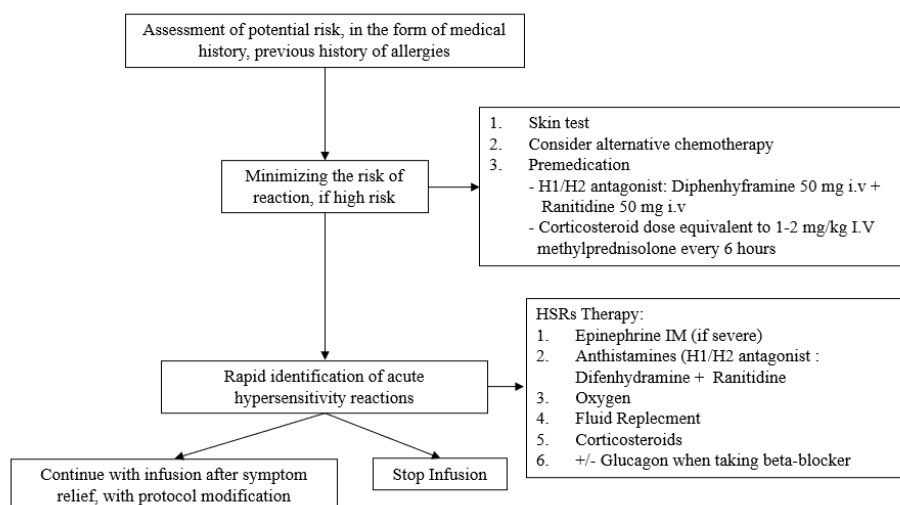


Figure 3. Premedication management and management of HSRs^{22,33,34}.

Premedication chemotherapy can help minimize the risk of hypersensitivity reactions in high-risk patients, such as in patients with comorbidities and in patients who do not have alternative chemotherapy³³. The use of premedication in the form of H1 blockers, H2 blockers, antileukotrienes, prostaglandin antagonists, corticosteroids can be considered for the prevention and treatment of IgE-mediated HSRs reactions (see Figure 1)^{9,35}.

DIPHENHYDRAMINE HYDROCHLORIDE

H1-blockers are commonly used to treat the symptoms of an allergic reaction. Histamine H1 receptor antagonists work by blocking the histamine H1 receptor (see figure 1)³⁶. First-generation H1-receptor antagonists include diphenhydramine, mepyramine, chlorpheniramine, promethazine, and cyproheptadine³⁷.

Diphenhydramine HCL has the chemical name 2-(diphenylmethoxy)-N,N-dimethyl-, Hydrochloride, with the chemical structure C₁₇H₂₁NO.HCl³⁸. Intravenous diphenhydramine 50 mg, pharmacokinetic parameters include a total clearance of 6.16 mL/min/kg, volume of distribution 4.54 L/kg, and a half-life of 8.5 hours³⁹.

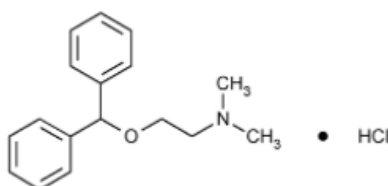


Figure 4. Chemical Structure of Diphenhydramine HCl (USP 2018).

Diphenhydramine is an over-the-counter drug, and is a first-generation antihistamine. The dose of diphenhydramine for allergy management in adults is 25-50 mg PO/IM/IV every 2 to 6 hours if needed. Maximum 300 mg/day orally, and increased by 100 mg to 400 mg/day IM/IV ¹¹.

RESULT

DIPHENHYDRAMINE AS A CHEMOTHERAPY PREMEDICATION

Chemotherapy agents have a mechanism of action that does not only affect cancer cells. However, it also affects other cells, to a greater or lesser degree ⁴¹. Thus, the use of chemotherapeutic agents has the potential to cause hypersensitivity reactions and toxic effects ⁴. Correct identification of HSRs and their toxic effects and appropriate management of their treatment with the use of chemotherapeutic agents, regardless of allergic or nonallergic reactions, are very important in the treatment of patients especially when suitable alternatives are not available or tolerated and delaying treatment continuation can be life-threatening ³³.

One approach used to overcome HSRs from the use of chemotherapeutic agents is the use of H1 antagonists (Diphenhydramine) ⁹. The use of diphenhydramine before chemotherapy is considered to be able to reduce the risk of developing HSRs, and minimize the toxic effects. HSRs can occur in both immediate and delayed reactions, with symptoms such as allergic nasal rhinitis, erythema, soft tissue angioedema, asthma, or hypoxia known as anaphylaxis ^{26,29,42}.

Several studies, case reports, and guidelines related to the use of diphenhydramine as a premedication before chemotherapy in various cancer conditions, and types of chemotherapeutic agents have shown varying results regarding their effectiveness in treating HSR reactions and reducing the risk of toxicity as shown in table 2.

Table 2. Diphenhydramine as a premedication of chemotherapeutic agents

Author, Year, Method	Chemotherapy Agent	Patient (Condition)	Dosage and directions for use	Manifestations (Intervention)	Time	Preventive outcome
(Jerzak et al. 2018) ⁴³ . Retrospective Cohort	Carboplatin 6th cycle or more	In adult women with ovarian cancer to treat HSRs	Diphenhydramine 50 mg IV, Dexamethasone 20 mg IV, and oral serotonin.	450 women received 6 cycles, 291 were given premedication	Premedication was given 30 minutes before carboplatin administration	Diphenhydramine did not significantly reduce HSRs on carboplatin
(Choi, McBride, and Scott 2019) ⁴⁴ Case Report	Nivolumab 2nd cycle	Hepatocellular carcinoma patients to treat Infusion Reaction (IR)	Diphenhydramine 25 mg orally and hydrocortisone 100 mg IV	The patient has a flushed face and shortness of breath with low back pain	30 minutes after administration of IR therapy the nivolumab infusion has been resumed	After administration of therapy to treat IR the patient can tolerate the administration of Nivolumab
(Moore et al. 2020) ⁴⁵ Retrospective	Daratumumab 1st cycle	Multiple myeloma patients to treat IRR (Infusion-related reaction)	Diphenhydramine, Acetaminophen, and corticosteroids	141 patients received daratumumab and all were given premedication	30-60 minutes before the first dose	Diphenhydramine shows efficacy for the management IRR with daratumumab.
(Durham et al. 2019) ⁴⁶ Study Retrospective	Paclitaxel, cetuximab, rituximab 1st to 3rd cycle	Patients with various types of cancer to cope with HSRs . reaction	Cetirizine 10 mg PO or diphenhydramine 50 mg PO or IV, and additionally acetaminophen 650 mg PO before rituximab, and famotidine 20 mg IV and dexamethasone 20	219 patients, 95 patients were given cetirizine (10 mg PO) and 124 patients were given diphenhydramine (50 mg PO/IV).	Administration is given before the first to third cycle, 30-60 minutes before the infusion starts	HSR reactions in 3 cycles in patients with the cetirizine group (19.3%) were lower than those in the diphenhydramine group (24.2%), and the highest HSRs reactions were

			mg IV before paclitaxel			caused by rituximab (61.95%), paclitaxel (33.9%), and cetuximab (4.15%).
(Hamano et al. 2021) ⁴⁷ Retrospective cohort	Cisplatin	In solid tumor conditions to prevent toxicity to the kidneys	Diphenhydramine	49 patients were not taking diphenhydramine and 49 were taking diphenhydramine.	Diphenhydramine is given 10 minutes before and 8 hours after the infusion	The potential for AKI in patients taking diphenhydramine was lower (6.1%) compared to those not taking diphenhydramine (22.4%). compared to those using
(Zhou et al. 2018) ⁴⁸ Guideline Review	311 chemotherapeutic agents in the NCCN guidelines	Potentially Inappropriate Medication (PIM) in hematological cancer as antiemetic prophylaxis	Diphenhydramine as an antiemetic 25-50 mg orally or IV every 4-6 hours with a maximum dose of 50-100 mg.	PIM analysis in the NCCN antiemetic guide of 311 lists of chemotherapeutic agents used in hematological cancer	Diphenhydramine is given every 4-6 hours during chemotherapy	123 chemotherapeutic agents (39.5%) recommended the use of diphenhydramine as supportive therapy in hematological cancer patients.
(Touma et al. 2014) ⁴⁹ Retrospective	Cetuximab 1st cycle	Head and neck cancer patients to treat Infusion Reactions (IR)	Diphenhydramine 50 or 25 mg IV., famotidine 20 mg IV., nebulizer albuterol 2.5 mg, hydrocortisone 100 mg, dexamethasone IV. (4-20 mg).	Comparison of diphenhydramine alone and the use of diphenhydramine in combination with albuterol, famotidine, with or without corticosteroids.	Given for 30-60 minutes	Diphenhydramine in combination showed a smaller IR reaction (1%), compared to diphenhydramine alone (31.8%).
(Castells et al. 2008) ⁴² Retrospective	<ul style="list-style-type: none"> • Cisplatin • Carboplatin • Oxaliplatin • Paclitaxel • Liposomal doxorubicin/ • Doxorubicin / Rituximab 	Patients undergoing chemotherapy and showing HSR reactions immediately or within 48 hours of infusion	Diphenhydramine/hydroxyzine 25 mg PO or IV, famotidine 20 mg IV or ranitidine 50 mg PO or IV, lorazepam 0.5-1 mg for anxiety	In 413 patients with various types of chemotherapy for evaluation of the premedication protocol for HSRs made previously.	Premedication was given 20 minutes before chemotherapy	The premedication protocol provided showed a reduced risk of HSRs of varying severity. 67% of them did not show HSR, 27% moderate reactions and 6% severe reactions.
(Comer and Cardwell 2017) ⁵⁰ Case Report	Brentuximab vedotin 2nd cycle	Refractory Hodgkin lymphoma patient to treat Infusion Reaction (IR)	Diphenhydramine 25 mg & 50 mg IV., famotidine 20 mg IV., Hydrocortisone 50 mg and 100 mg IV.	The patient showed an IR condition in the form of shortness of breath, and chest pain after giving the 2nd cycle, then he was given diphenhydramine, famotidine, and hydrocortisone.	Treatment was given within 30 minutes of starting brentuximab, and symptoms began to subside after 30 minutes of treatment.	The patient's condition improved temporarily after administration of IR therapy. However, symptoms arise in the form of tingling and numbness in the feet and tongue.
(Tsavaris et al. 1991) ⁵¹ Randomized clinical trial	Cisplatin 1st cycle	Cancer patients to treat nausea, vomiting after chemotherapy with a combination of metoclopramide	Metoclopramide 2 mg/kg every 2 hours for 5 IV doses, first dose of diphenhydramine 200 mg before cisplatin administration, and 100 mg after cisplatin	Of the patients receiving cisplatin, 44 were given metoclopramide alone, and 47 were given a combination of metoclopramide and	Metoclopramide was administered 30 minutes before cisplatin, 90, 210, 330, 450 minutes after cisplatin. Diphenhydramine 30 minutes before, and 330,	The administration of diphenhydramine as an adjuvant for nausea and vomiting did not show a significant difference with the comparison of

			administration.	diphenhydramine.	690, 1050 minutes after cisplatin	metoclopramide alone.
(Hattori et al. 2019) ⁵² Retrospective	Ramucirumab	Patients with solid tumors, to see the safety of Infusion Related Reaction (IRR) without Antihistamines	H1 antihistamines and steroids	51 patients received ramucirumab, 42 patients received premedication and 9 without premedication	-	There is no IRR in patients without antihistamines, and may be a good choice in patients avoiding the sedative effects of H1 antihistamines.
(Yamada et al. 2001) ⁵³ Kaplan-Meier	Paclitaxel	Patients with advanced gastric cancer to prevent HSRs reaction	Diphenhydramine 50 mg PO., ranitidine 20 mg IV., dexamethasone 50 mg IV.	60 patients were given paclitaxel by 3-hour infusion and given short-term premedication	30 minutes before administration of chemotherapeutic agents	Paclitaxel infusion for 3 hours is considered safe with the use of short-term premedication.
(Quock et al. 2002) ⁵⁴ Retrospective	Paclitaxel 1st cycle	Cancer patients to prevent reactions of HSRs after weekly administration	Diphenhydramine 25 mg, cimetidine 300 mg, dexamethasone 10 mg IV.	30 patients receiving weekly paclitaxel for 1 hour given premedication	30 minutes before paclitaxel	Giving premedication in the first cycle of paclitaxel, can overcome paclitaxel without repeated HSR on continued weekly administration.
(Kidera et al. 2011) ⁵⁵ Retrospective Cohort	Oxaliplatin 6th cycle	Colorectal cancer patients to prevent HSRs	Diphenhydramine 50 mg PO., dexamethasone 8 mg and 20 mg, granisetron 3 mg and famotidine 20 mg	181 colorectal patients were premedicated with dexamethasone, granisetron in the first cycle and modified premedication in the 6th cycle with the addition of diphenhydramine and famotidine. As well as increasing the dose of dexamethasone to 20 mg.	Initial premedication 15 minutes before oxaliplatin, Modified premedication 30 minutes before oxaliplatin	16 incidents of HSR on initial premedication, and decreased to 7 incidents of HSR after HSR modification. Increasing the dose of dexamethasone and antihistamines significantly reduced the incidence of HSR in patients receiving Oxaliplatin.

Currently, there have been many clinical trials related to the efficacy of using diphenhydramine in patients receiving chemotherapy, both as a premedication and as a therapy to treat the adverse effects of chemotherapy. Tests conducted by Yamada related to the safety of using paclitaxel infusion for 3 hours with short-term premedication. Premedication given included diphenhydramine, ranitidine and dexamethasone 30 minutes before paclitaxel infusion in patients with advanced gastric cancer. The results showed that infusion of paclitaxel for 3 hours was considered safe and did not cause HSRs with the use of premedication⁵³. Castells also conducted a study, related to premedication protocols in chemotherapy patients by observing the reaction of HSRs immediately or within 48 hours after infusion. The use of diphenhydramine/hydrocortisone 25 mg PO or IV with a combination of famotidine 20 mg IV or ranitidine 50 mg PO or IV, and lorazepam 0.5-1 mg showed a reduced risk of HSRs with the use of taxane, platinum and antibiotics chemotherapeutic agents (Table 2)⁴².

In most studies related to the prevention and treatment of HSR, IR used a regimen of diphenhydramine, dexamethasone, famotidine/cimetidine/ranitidine as premedication (see Figure 1). The use of premedication using this regimen has shown effective results in reducing the incidence and overcoming more severe HSR and IR reactions than the use of various types of chemotherapy agents^{45,46,49,54,55}. Research related to the efficacy of premedication is generally carried out in patients receiving chemotherapy agents from the taxane group, platinum, monoclonal antibodies, anthracyclines (Table 2). This is supported by the statement that the highest chemotherapeutic agents cause HSRs, IRs from the Taxane, L-asparaginase, Platinum, doxorubicin, procarbazine, etoposide, teniposide, and cytarabine groups^{4,20-22}

In addition to the reduced risk of HSRs from the administration of chemotherapeutic agents. A retrospective study showed that giving diphenhydramine before giving cisplatin could reduce the severity of kidney damage, compared to those who did not receive diphenhydramine as indicated by the results of the renal profile examination⁴⁷.

Research related to the efficacy of diphenhydramine as prophylactic adjuvant antiemetic in the use of cisplatin in the first cycle was carried out by Tsavaris, by comparing the use of metoclopramide alone and the use of metoclopramide with the addition of diphenhydramine showed insignificant results⁵¹. However, Diphenhydramine has been included in the NCCN guideline as antiemetic prophylaxis of 123 chemotherapy agents to treat Potentially Inappropriate Medication (PIM) in Hematological Cancer. In the NCCN guideline, diphenhydramine is combined with corticosteroids and PPIs as antiemetic prophylaxis due to chemotherapy⁴⁸.

However, in some cases and studies, the use of chemotherapy premedication with diphenhydramine regimen has no significant effect and temporary relief. Comer, et.al reported a case related to the use of diphenhydramine, famotidine and hydrocortisone therapy in a patient with refractory Hodgkin lymphoma to treat an infusion reaction (IR) that occurred after 30 minutes of administration of chemotherapy Brentuximab 2nd cycle. The patient's condition improved after 30 minutes, but symptoms occurred in the form of tingling and numbness in the feet and tongue⁵⁰. Jerzak's retrospective study also showed no significant difference in the reduction in the incidence of HSR in adult female patients with ovarian cancer who received the 6th cycle of cisplatin⁴³.

Premedication without using diphenhydramine was also carried out by Hattori, to avoid the sedative effect that could result from the use of H1 antihistamines in tumor patients taking Ramucirumab. The results showed that there was no IRR in patients without H1 antihistamines⁵². In addition to diphenhydramine, research related to the use of cetirizine as a substitute antihistamine related to the prevention of Infusion Reactions (IR) from the use of chemotherapy agents. The choice of cetirizine in the premedication regimen, because it has a milder sedative effect but still requires further studies regarding its efficacy and safety compared to the use of diphenhydramine⁴⁶.

DISCUSSION

Diphenhydramine is commonly used as a premedication before the use of chemotherapeutic agents^{9,22,33,34,56}. Diphenhydramine is a first-generation H1 antihistamine to treat IgE-mediated HSRs^{9,35}. Diphenhydramine works by inhibiting the stimulation of histamine H1 receptors. Inhibition of H1, can overcome the effects of bronchospasm, erythema, urticaria, edema, decreased arterial blood pressure which are generally clinical signs of cancer patients with HSRs (see Figure 2).

The dose of diphenhydramine which can be used as a premedication or treatment of HSRs is 25 mg or 50 mg given intravenously or orally, both before chemotherapy and when HSR or IR reactions occur^{42,50}. The use of diphenhydramine can be monotherapy, or in combination with other drugs, such as H2 antihistamines, corticosteroids, or anticonvulsants.

A number of studies have shown that diphenhydramine in chemotherapy premedication protocols has shown effective results as prevention and management of incidents related to HSRs, IR and adverse side effects. In particular, the use of chemotherapy has a high risk of HSR.

The use of diphenhydramine in some conditions can only temporarily overcome HSR, or the effect given is no significant difference. So that the initial assessment of the patient and appropriate treatment management is very important, to avoid the risk of HSRs, IR, and other effects (see Figure 3).

CONCLUSION

A number of related studies have shown that diphenhydramine, either as monotherapy or in combination, is effective in preventing HSRs, IR and reducing the risk of toxicity with the use of antineoplastic agents. The use of diphenhydramine as a chemotherapy premedication aims to minimize side effects or unwanted reactions during chemotherapy and can help improve the quality of life of patients undergoing chemotherapy treatment.

REFERENCES

1. Wilson BE, Jacob S, Yap ML, Ferlay J, Bray F, Barton MB. Estimates of global chemotherapy demands and corresponding physician workforce requirements for 2018 and 2040: a population-based study. *Lancet Oncol.* 2019;20(6):769-780. doi:10.1016/S1470-2045(19)30163-9
2. Giavina-Bianchi P, Patil SU, Banerji A. Immediate Hypersensitivity Reaction to Chemotherapeutic Agents. *J Allergy Clin Immunol Pract.* 2017;5(3):593-599. doi:10.1016/j.jaip.2017.03.015
3. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The different mechanisms of cancer drug resistance: A brief review. *Adv Pharm Bull.* 2017;7(3):339-348. doi:10.15171/apb.2017.041
4. Pagani M, Bavbek S, Alvarez-Cuesta E, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. *Allergy Eur J Allergy Clin Immunol.* 2022;77(2):388-403. doi:10.1111/all.15113
5. Gobel BH. Chemotherapy-Induced Hypersensitivity Reactions. 2005;32(5):1027-1035.
6. Syrigou E, Triantafyllou O, Makrilia N, et al. Acute hypersensitivity reactions to chemotherapy agents: An overview. *Inflamm Allergy - Drug Targets.* 2010;9(3):206-213. doi:10.2174/187152810792231887
7. NHSGGC. NHSGGC - Chemotherapy-induced hypersensitivity. Published online 2017. <https://www.clinicalguidelines.scot.nhs.uk/nhsggc-guidelines/nhsggc-guidelines/haematologyoncology/chemotherapy-induced-hypersensitivity/#:~:text=A hypersensitivity reaction can occur,on mast cells and basophils>.
8. Boulanger J, Boursiquot JN, Courmoyer G, et al. Management of hypersensitivity to platinum- and taxane-based chemotherapy: CEPO review and clinical recommendations. *Curr Oncol.* 2014;21(4):630-641. doi:10.3747/co.21.1966
9. Roselló S, Blasco I, García Fabregat L, Cervantes A, Jordan K. Management of infusion reactions to systemic anticancer therapy: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2017;28(Supplement 4):iv100-iv118. doi:10.1093/annonc/mdx216
10. Li H, Xiao Y, Li Q, et al. The allergy mediator histamine confers resistance to immunotherapy in cancer patients via activation of the macrophage histamine receptor H1. *PlumX Metrix.* 2021;40(1):35-52. doi:https://doi.org/10.1016/j.ccell.2021.11.002
11. Sicari V, Zabbo C. Diphenhydramine. StatPearls Publishing LLC; 2021.
12. Blaiss MS, Bernstein JA, Kessler A, et al. The Role of Cetirizine in the Changing Landscape of IV Antihistamines: A Narrative Review. *Adv Ther.*

13. Picard M. Management of Hypersensitivity Reactions to Taxanes. *Immunol Allergy Clin North Am.* 2017;37(4):679-693. doi:10.1016/j.iac.2017.07.004
14. ACS. How is Chemotherapy Used to Treat Cancer? 2019. Published online 2019:1-7. <https://www.cancer.org/content/dam/CRC/PDF/Public/8417.00.pdf>
15. Amjad MT, Anusha C, Anup K. Cancer Chemotherapy - StatPearls - NCBI Bookshelf. Published online 2021. <https://www.ncbi.nlm.nih.gov/books/NBK564367/>
16. Kalyn R, BC Cancer. Cancer drug pharmacology table. BC cancer Pharm Educ Progr. Published online 2021:1-9.
17. Travor. K. Cancer Chemotherapy : Introduction High - Yield Terms to Learn Cancer Cell Cycle Kinetics Cell Cycle Kinetics Cell Cycle Kinetics The Log - Kill Hypothesis. *Cancer Chemother Introd.* Published online 2022:1-17.
18. Regnard C, Kindlen M. Chemotherapy: side effects. *Support Palliat Care Cancer.* Published online 2019:39-41. doi:10.1201/9781315378596-13
19. NHS. Side effects -Chemotherapy. Published online 2020. <https://www.nhs.uk/conditions/chemotherapy/>
20. Weiss RB. Hypersensitivity reactions. *Semin Oncol.* 1992;19(5):458-477. <http://europepmc.org/abstract/MED/1384149>
21. Loughlin, Kevin, R.; Generali J. Prescription Drugs: Alternative Uses, Alternative Cures: Over 1,500 New Uses for FDA-Approved Drugs. (Joyce Generali KRL, ed.). Pocket Books; 2007. https://www.google.co.id/books/edition/Prescription_Drugs_Alternative_Uses_Alte/UGqjFPQ_LkgC?hl=id&gbpv=1&dq=prescription+drugs:+alternative+uses,+alternative+cures:+over+1,500+new+uses&printsec=frontcover
22. Faisal A, Sanchez LDLV., Gilbert L., Copaescu AM., Isabwe GAC. Premedication Protocols to Prevent Hypersensitivity Reactions to Chemotherapy: a Literature Review. *Clin Rev Allergy Immunol.* 2022;62:534-547. doi:10.1007/s12016-022-08932-2
23. Franceschini F, Bottau P, Caimmi S, et al. Mechanisms of hypersensitivity reactions induced by drugs. *Acta Biomed.* 2019;90(2):44-51. doi:10.23750/abm.v90i3-S.8160
24. Vogel WH. Infusion Reactions: Diagnosis, Assessment, and Management. *Clin J Oncol Nurs.* 2010;14(2). doi:10.1188/10.CJON.E10-E21
25. Justiz Valiant A, Vashisht RZ. Immediate Hypersensitivity Reactions. *StatPearls Publishing;* 2021. https://www.ncbi.nlm.nih.gov/books/NBK513315/#_NBK513315_pubdet_
26. Baldo BA, Pham NH. Drug Allergy : Mechanisms of Hypersensitivity. Vol 37-90. Springer Science+Business Media, LLC; 2013. doi:doi: 10.1007/978-1-4614-7261-2_3
27. Abbas, M.; Moussa, M.; Akel H. Type I Hypersensitivity Reaction. *StatPearls [Internet];* 2022. https://www.ncbi.nlm.nih.gov/books/NBK560561/#_NBK560561_pubdet_
28. Gell PGH, Coombs RRA. *Clinical Aspects of Immunology.* In: Second Edi. Blackweel Scientific Publication; 1968:580.
29. Dispenza MC. Classification of hypersensitivity reactions. *Allergy Asthma Proc.* 2019;40(6):470-473. doi:10.2500/aap.2019.40.4274
30. Thangam EB, Jemima EA, Singh H, et al. The role of histamine and histamine receptors in mast cell-mediated allergy and inflammation: The hunt for new therapeutic targets. *Front Immunol.* 2018;9(AUG):1-9. doi:10.3389/fimmu.2018.01873
31. Picard M, Matulonis UA, Castells M. Chemotherapy hypersensitivity reactions in ovarian cancer. *J Natl Compr Canc Netw.* 2014;12(3):389-402. doi:10.6004/jnccn.2014.0040
32. Hong DI, Madrigal-Burgaleta R, Banerji A, Castells M, Alvarez-Cuesta E. Controversies in Allergy: Chemotherapy Reactions, Desensitize, or Delabel? *J Allergy Clin Immunol Pract.* 2020;8(9):2907-2915.e1. doi:10.1016/j.jaip.2020.08.005
33. Tham EH., Cheng YK., Tay MH., Alcasabas AP., Shek LOC. Evaluation and Management of Hypersensitivity Reactions to Chemotherapy Agents. Published online 2015:145-150. doi:http://dx.doi.org/10.1136/postgradmedj-2014-132686
34. Clemmons, Amber G, Arpita C, et al. Premedications for Cancer Therapies: A Primer for the Hematology/Oncology Provider. *J Adv Pract Oncol.* 2021;12(8):810-832. doi:10.6004/jadpro.2021.12.8.4
35. Broyles AD, Banerji A, Castells M. Practical Guidance for the Evaluation and Management of Drug Hypersensitivity: General Concepts. *J Allergy Clin Immunol Pract.* 2020;8(9):S3-S15. doi:10.1016/j.jaip.2020.08.002
36. Groth CM, Acquisto NM. H1-Blockers. *Encycl Toxicol Third Ed.* 2014;2:809-812. doi:10.1016/B978-0-12-386454-3.000713-2
37. Hill SJ, Baker JG. Histamine receptors. *Encycl Biol Chem.* Published online 2004:378-383. doi:doi.org/10.1016/B0-12-443710-9/00309-4
38. USP29. USP Monographs: Diphenhydramine Hydrochloride. Published online 2016. http://www.pharmacopeia.cn/v29240/usp29nf24s0_m27130.html
39. Blyden GT, Greenblatt DJ, Scavone JM, Shader RI. Pharmacokinetics of Diphenhydramine and a Demethylated Metabolite Following Intravenous And Oral Administration. *J Clin Pharmacol.* 1986;26(7):529-533. doi:10.1002/j.1552-4604.1986.tb02946.x
40. USP. DIPHENHYDRAMINE. 2018;(May).
41. Prieto-Callejero B, Rivera F, Fagundo-Rivera J, et al. Relationship between chemotherapy-induced adverse reactions and health-related quality of life in patients with breast cancer. *Medicine (Baltimore).* 2020;99(33):e21695. doi:10.1097/MD.00000000000021695
42. Castells MC, Tennant NM, Sloane DE, et al. Hypersensitivity reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol.* 2008;122(3):574-580. doi:10.1016/j.jaci.2008.02.044
43. Jerzak KJ, Deghan Manshadi S, Ng P, et al. Prevention of carboplatin-induced hypersensitivity reactions in women with ovarian cancer. *J Oncol Pharm Pract.* 2018;24(2):83-90. doi:10.1177/1078155216679028
44. Choi B, McBride A, Scott AJ. Treatment with pembrolizumab after hypersensitivity reaction to nivolumab in a patient with hepatocellular carcinoma. *Am J Heal Pharm.* 2019;76(21):1749-1752. doi:10.1093/ajhp/zxz189
45. Moore DC, Arnall JR, Thompson DL, et al. Evaluation of Montelukast for the Prevention of Infusion-related Reactions With Daratumumab. *Clin Lymphoma, Myeloma Leuk.* 2020;20(10):e777-e781. doi:10.1016/j.clml.2020.05.024
46. Durham CG, Thotakura D, Sager L, Foster J, Herrington JD. Cetirizine versus diphenhydramine in the prevention of chemotherapy-related hypersensitivity reactions. *J Oncol Pharm Pract.* 2019;25(6):1396-1401. doi:10.1177/1078155218811505
47. Hamano H, Ikeda Y, Goda M, et al. Diphenhydramine may be a preventive medicine against cisplatin-induced kidney toxicity. *Kidney Int.* 2021;99(4):885-899. doi:10.1016/j.kint.2020.10.041
48. Zhou A, Holmes H, Hurria A, Wildes T. Inclusion of medications considered potentially inappropriate in older adults in chemotherapy templates for hematologic malignancies: one recommendation for all? *HSS Public Access.* 2018;35(5):139-148. doi:10.1007/s40266-018-0538-2
49. Touma W, Koro S, Ley J, et al. Risk Factors for and Pre-medications to Prevent Cetuximab-Induced Infusion Reactions in Patients with Squamous Cell Carcinoma of the Head and Neck. *NIH Public Access.* 2014;50(9):895-900. doi:10.1016/j.jor.2014.06.017.Risk
50. Comer H, Cardwell K. Brentuximab Vedotin Infusion Reaction Management: A Case Study. *J Adv Pract Oncol.* 2017;8(6):626-629. doi:10.6004/jadpro.2017.8.6.5
51. Tsavaris N., Zamanis N., Zinelis A., et al. Diphenhydramine for Nausea and Vomiting Related to Cancer Chemotherapy with Cisplatin. *J pain symptom Manag.* 1991;6(8):461-465.
52. Hattori N, Yamaguchi T, Kodama H, et al. The safety of ramucirumab without H1-antihistamines as a premedication in patients with solid cancers: A retrospective study. *Ann Oncol.* 2019;30(November):ix148-ix149. doi:10.1093/annonc/mdz434.031
53. Yamada Y, Shiaro K, Ohtsu A, et al. Phase II trial of paclitaxel by three-hour infusion for advanced gastric cancer with short premedication for prophylaxis against paclitaxel-associated hypersensitivity reactions. *Ann Oncol.* 2001;12:1133-1137. doi:10.1023/A
54. Quock J, Dea G, Tanaka M, Gandara D, Lara P, Lau D. Premedication Strategy for Weekly Paclitaxel. *Cancer Invest.* 2002;20(5-6):666-672. doi:<https://doi.org/10.1081/CNV-120003535>
55. Kidera Y, Satoh T, Ueda S, et al. High-dose dexamethasone plus antihistamine prevents colorectal cancer patients treated with modified FOLFOX6 from hypersensitivity reactions induced by oxaliplatin. *Int J Clin Oncol.* 2011;16(3):244-249. doi:10.1007/s10147-010-0170-6