Open Access

Review Article

Desensitization Protocols for Hypersensitivity Induced by Cytotoxic Drugs; Platinum Salts and Taxanes

Maha Zahid, Husnain Hamid, Numra Tahir, Aqsa Amjad, Irfan Bashir, Muhammad Jamshaid

Faculty of Pharmacy, University of Central Punjab, Lahore Pakistan

ABSTRACT

With the expanding use of Platins and Taxanes for cancer patients, a highly concerning threat is observed in the form of Hypersensitivity reactions. To reduce hypersensitivity reactions, different desensitization protocols are formed. The prevalence of hypersensitivity to carboplatin ranges from 1-27%, oxaliplatin 1-19%, cisplatin 5-20%, and docetaxel 10-20%. Even though the hypersensitivity reactions following the administration of oxaliplatin may be less severe than carboplatin hypersensitivity reactions but extremely life-threatening reactions have been observed also. Some patients, allergic to oxaliplatin show uncharacteristic hypersensitivity signs such as chills, fever, and abdominal and/or extreme chest pain. Symptoms followed by Taxanes induced hypersensitivity reactions are flushing, pruritus, and skin rashes to more life-threatening features like dyspnea, hypotension, angioedema, and occurrence generalized pale red bumps on the skin which is also called as urticarial. Numerous preventive methods have been develop to avoid hypersensitivity reactions and the most effective technique so far is the rapid drug desensitization. It allows re-exposure to the culprit drug safely and effectively. Drug desensitization is a whole set of techniques or process by which an offender drug is introduced in the system of a patient following a cycle of very calculated dose augmentation, in a way that the total administered dose is equal to the actual target dose of the drug. Introduced protocols result in better outcomes as expected and now used widely throughout hospitals accordingly.

Keywords: Cytotoxic agents, Desensitization protocols, Hypersensitivity reactions.

How to Cite This Article: *Maha Zahid, Husnain Hamid, Numra Tahir, Aqsa Amjad, Irfan Bashir, Muhammad Jamshaid. Desensitization Protocols for Hypersensitivity Induced by Cytotoxic Drugs; Platinum Salts and Taxanes. Pak Armed Forces Med J 2025; 75(Suppl-1): S128-S132. DOI: https://doi.org/10.51253/pafmj.v75iSUPPL-1.4327*

BACKGROUND

Cancer can be transformed into many different forms based on the locality of occurrence, source of the cancer cells, and range of genetic mutation and influence therapeutic response.[1] Chemotherapeutic agents form an extensive range of drugs just as taxanes, methotrexate, etoposide, and platinum agents (Platins) used for cancer treatment.[2] Cancer patients need to proceed with the therapy because the drug responsible for the adverse reaction is mostly the highly efficacious one for their disease.[3] Hypersensitivity reaction (HSR) to a chemotherapeutic drug can occur while the administration of a drug or even after administration. Symptoms included are reddening of the skin, change in vital signs, hyperventilation, backaches, high fever, skin rashes, and nausea.[4] Patients who suffer from allergic reactions have a possibility of quitting first-line therapy and shifting towards a second-line therapy that is usually less efficacious.[5] Hypersensitivity to platins and taxanes is not a unique occurrence. These allergic responses to platins are thought to be immunoglobulin E induced whereas in the case of taxanes release of mast cells and basophils occurs.[6] To reduce HRs, different desensitization protocols formed vary upon physician understandings.[7] In the current review, it was aimed to form literature, indicating available desensitization protocols.

Correspondence: Dr Husnain Hamid , Faculty of Pharmacy, University of Central Punjab, Lahore Pakistan

Received: 17 May 2020; revision received: 02 Jul 2020; accepted: 09 Jul 2020

Prevalence of Platins and Taxanes induced HSR's

Hypersensitivity reactions to various cytotoxic agents can lead to the withdrawal of a standard certified first choice of therapy. The occurrence of hypersensitivity to carboplatin ranges from 1-27%, oxaliplatin 1-19%, cisplatin 5-20%, and docetaxel 10-20%.[8] The research reported carboplatin HSRs to take place in 16 % of patients with ovarian cancer and 27% of patients being treated with more than seven infusions.[9] Zanotti *et al.*, have reported that the patients who receive more than seven infusions of carboplatin have an incidence of adverse effects that ranges up to 27%.[10] In another study conducted in 2001 which included 194 adults being treated for the first time with carboplatin for ovarian cancer; out of which 16% developed signs and symptoms which were closely related to hypersensitivity reactions.[11]

HSRs following cisplatin are presently rare because of its less consumption but when consumed in combination with radiotherapy; the hypersensitive reactions may be up to 16%.[12]

Paclitaxel is used mainly for lung, breast, and gyne related malignant tumors. Docetaxel is a recently discovered semisynthetic taxane. In initial testing or phase I testing of paclitaxel, the instant HSRs usually occurred in an enormous proportion of patients typically following their first-ever contact. In patients, who were pre-medicated according to the typical or simple plan; the incidence of HSR following paclitaxel was 10%.[13]

Anaphylaxis after Platins

The HSRs of platinum-based compounds are represented by type I of hypersensitivity reaction which is characterized by red welts on the skin that itch intensely, rash, narrowing of bronchi, and hypotension.[14] After the 6th cycle of exposure to platins, the danger of anaphylaxis elevates and persists to elevate up to the 8th cycle as the cumulative risk reaches 19.5%.[15] Some patients with oxaliplatin reactivity exhibit unusual symptoms of hypersensitivity, such as cold, pyrexia, abdominal and/or severe chest pain reactive to oxaliplatin show unusual hypersensitivity signs such as cold, pyrexia, abdominal, and/or extreme chest pain.[16]

Anaphylaxis after Taxanes

Symptoms followed by taxane-induced HSRs are flushing, pruritus, and skin rashes to more life-threatening features like dyspnea, hypotension, angioedema, and occurrence generalized pale red bumps on the skin which is also called as urticarial.[17] There have been only a small number of conflicting reports of ruthless life-endangering skin allergies with docetaxel, and even lesser with paclitaxel. Both paclitaxel and docetaxel can lead to drug-induced lupus erythematosus (DILE), which most frequently displays as minor cutaneous lupus erythematosus. Though, "rashes" is a common term, particularly with docetaxel. The clinical indications have got little attention in the literature. Lately, the general incidence of taxane-induced nail destruction has been analytically investigated.[18]

DESENSITIZATION

Various managing proposition has been established to avoid HSRs and rapid drug desensitization (RDD) has appeared as an efficient management technique that permits the re-exposure to the culprit drug.[19] Desensitization is indicated even because patients have no option of HSRs triggered by mast cell activation due to their most effective first line therapy. Desensitization is accomplished by stepwise increasing the minimal doses of the offender drug until the desired dose is attained.[20] Protocols for desensitization characteristically involves the stepwise increase in the administration of allergen medicine with no life-threatening symptoms.[21]

Rapid Drug Desensitization

Drug desensitization is a whole set of techniques or process by which an offender drug is introduced in the system of a patient following a cycle of very calculated dose augmentation, in a way that the total administered dose is equal to the actual target dose of the drug.[22] The manifestations of RDD are: (1) No substitute drug is available; (2) The offending drug is more efficacious (3) The offending drug has an exceptional mechanism of action.[23] Rapid Drug Desensitization (RDD) is a technique through which mast cells are left insensitive to an allergic agent by providing short-term tolerance for the hypersensitive patients thereby, preserving them from anaphylaxis.[24]

As RDD leads to temporary insensitivity, patients require to be desensitized before every exposure with the culprit medication.[25] Some researches show that premedication is of no use with platinum drugs, but in the case of taxanes; premedication can eliminate the possibility of HSRs.[26] It is significant to highlight that successful implementation of the desensitization procedure is dependent upon the expertise of a group of health care professionals responsible for its administration.[27] A multi-step protocol for desensitization can be carried out if the skin test is positive for platinum-containing compounds or if therapy cannot be replaced and if ceasing therapy would risk the patient's life.[28]

Infusion time

Hypersensitivity reactions as a result of exposure to platinum salts are usually constant with type 1 hypersensitivity that occurs after numerous series of treatments. Reaction to taxanes and clonal antibodies causes related indication, however, they are usually immediate, taking place throughout the initial few minutes of the first or second infusion. About, 10%-30% of anti-cancers responses are delayed and may occur in subsequent infusions, thus showing the value of patient vigilant evaluation before and after administration. Less severe reactions can be controlled by a brief disruption of infusion, a decrease of the

infusion rate, and management of symptoms. Re-exposure can be considered after the complete management of all symptoms.[29] The administration of carboplatin in the form of an infusion over 3 hours in conjunction with premedication decreased the hypersensitivity hazard from 21% to as low as 3.4%.[30] A systematic review assessed the effect of infusion time for paclitaxel and exhibited no variation in the onset of hypersensitivity when the infusion was administered over an extended period that is 3 or 24 hours.[31]

Premedication

Pretreatment decreases the incidence of paclitaxel hypersensitivity reactions although another report notes that 41% of patients who reacted did so despite pretreatment. One of the commonly used pretreatment protocol is 40 mg of dexamethasone or equal dose is given per os (PO) 12 hours and 6 hours before the administration of paclitaxel along with diphenhydramine and an antihistamine 30 min before the infusion. With the help of this pretreatment, the rate of reaction is usually 1–2% compared to 2–5% without pretreatment.[32] Recently, however, 132 patients were treated with only 10–20 mg of dexamethasone immediately before infusion, with no increase in the reaction rate. The premedication regime used for hypersensitivity to paclitaxel consist of 20 mg of dexamethasone (steroid) administered either orally or by parenteral route (intravenously) between 12 and 6 hours before infusion drug, 50mg of antihistamine (diphenhydramine) and 50 mg of ranitidine intravenously 30 minutes beforetreatment.[33] A simple regimen of premedication comprising of only one IV or oral steroid dose (10 mg), given half-hour before paclitaxel administration.[13] The premedication protocol for docetaxel is not similar to that of paclitaxel. Patients being treated with docetaxel need dexamethasone, 16 mg/d for 3 days whereas those being treated with paclitaxel receive dexamethasone, 20 mg at 12 and 6 hours before drug administration besides with diphenhydramine 50 mg, cimetidine 300 mg or ranitidine 50 mg or both given through IV route 30 to 60 minutes beforeadministration.[34]

Desensitization protocol of Platins and Taxanes

Various protocols for desensitization have been effectively used to handle HSRs to taxanes and platinum-containing compounds.[35] In available plans, the initiating dose varies from 1/10000 to 1/100 of the complete effective dose. The initial amount to be administered should be calculated in light of the relentlessness of the reactions. In patients with a past medical history of severe anaphylaxis, the starting dose must range between 1/1000 000 and 1/10 000 of the complete therapeutic dose.[36] Patients who in the past, have experienced harsh hypersensitivity reactions towards the administered compound, or who have experienced HSRs earlier in the regular 12-step desensitization might come across milder reactions if desensitized with a 16- step protocol, in which another infusion bag is added containing 1/10,000 dilution of the complete therapeutic dose.[37] The 12-step desensitization protocol was designed by the Dana–Farber Cancer Institute and the Brigham and Women's Hospital.[38] Research conducted claims that in contrast to the majority of other protocols, it is the only one that has been productively utilized for the desensitization of many anti-cancer agents. This protocol involves the preparation of three separate solutions with a rising concentration of the chemotherapy agent. The speed of infusion changes after every 15 minutes and the amount of drug-infused is rough, twice the volume of earlier step. As published in three research papers, the use of 12-step protocol leads to either no HSRs or a mild reaction as compared to the original reaction that necessitated desensitization.[27]

Two researchers namely Castells and Limsuwan in 2008 and 2010 declared the outcomes of desensitization for platins (oxaliplatin, carboplatin, and cisplatin) and taxanes (paclitaxel).To be included in the study, patients must have had a hypersensitivity reaction for the duration of infusion or within 48 hours following infusion. As a result of every desensitization carried out, 94% of patients experienced placid or no reaction. Placid responses were managed by stopping the administration of anticancer agents and giving suitable medication to overcome the hypersensitive reactions. On average, 7% of reactions appeared during steps 1–4, 18% during steps 5–8, and 75% between steps 9–12, with 51% of reactions appearing during the final step of the desensitization protocol. All patients got their treatment at a complete dose.[38, 39]

In 2005, R Confino-Cohen performed 6-hour drug desensitization which contained 4 carboplatin infusions. The initial 3 infusion bags carried 1:1000, 1:100, and 1:10 of the final amount which was diluted in 150 mL of D5W (Dextrose 5 water) solution. The final infusion bag had the remaining of the unadulterated drug. Every dilution was administered

in infusion over 90 minutes, starting with the 1/1000 solution. After that elevated concentration was administered right away following the successful conclusion of the prior infusion. Patients received premedication comprising of antiemetics (ondansetron hydrochloride) and dexamethasone as prescribed for regular carboplatin chemotherapy. The exact procedure was carried out in all upcoming treatments with carboplatin.[40] The desensitization procedure which was effectively carried out in a case study included the following procedure. Four successive dilutions (1:10,000, 1:1,000, 1:100, and 1:10) of the complete oxaliplatin dose were constituted in 100 ml dextrose 5% in water (D5W). Initiating with the least dose (bag 1), each dilution was administered over 60 minutes with cautious monitoring of vital signs. The final infusion bag (bag 5), containing 90% of the total dose to be administered in 500 ml D5W, was then administered over 2 hours. Mild or no HSRs were observed.[4]

Desensitization for taxanes is usually accepted by patients. In a trial of 17 patients who received overall 77 desensitization to paclitaxel or docetaxel, out of which 72 de sensitizations were completed devoid of any reactions. Four patients had 5 reactions in the process of desensitization, all of which were less intense than their earlier reactions. Contrarily, 5 patients who experienced re challenge (i.e. administration of the offender taxane by regular infusion) earlier to desensitization had to face recurring reactions, despite premedication and a decreased infusion rate27.

The breakthrough of HSRs took place in six patients (27 %) in a totality of nine trials (8 %). No more than one HSR was harsh and linked with hypo-tension, but all desensitization protocol allowed the administration of the final dose. Also, two desensitization to docetaxel was carried out in one patient without incident. In research on 413 desensitization that chiefly involved platins and taxanes, 28 patients underwent 140 intravenous (IV) and 12 intra peritoneal (IP) desensitization protocol to paclitaxel. A significant finding was that breakthrough reactions happened during the initial desensitization and that their occurrence radically decreased after that. These responses were all less extreme than the initial HSR, and only one was treated with epinephrine.[39]

CONCLUSION

Platins and Taxanes are widely used cytotoxic agents but result in many hypersensitive reactions lead to anaphylaxis and death of the patient. With ongoing development in healthcare field medical professionals, introduced different therapeutic protocols to minimize these reactions and improve the therapeutic management of chronic diseases. Introduced protocols result in better outcomes as expected and now used widely throughout hospitals accordingly.

Conflict of Interest: None.

Funding Source: None.

Authors Contributions:

Following authors have made substantial contributions to the manuscript as under:

MZ & HH: Data acquisition, critical review, approval of the final version to be published.

NT & AA: Conception, study design, drafting the manuscript, approval of the final version to be published.

IB & MJ: Data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Weinstein JN, Collisson EA, Mills GB, Shaw KRM, Ozenberger BA, Ellrott K, et al. The cancer genome atlas pan-cancer analysis project. Nat Genet 2013; 45(10): 1113-20.
2. Altwerger G, Florsheim EB, Menderes G, Black J, Schwab C, Gressel GM, et al. Impact of carboplatin hypersensitivity and desensitization on patients with recurrent ovarian cancer. J Cancer Res Clin Oncol 2018; 144(12): 2449-56.
3. Herrero T, Tornero P, Infante S, Fuentes V, Sanchez M, De Barrio M, et al. Diagnosis and management of hypersensitivity reactions caused by oxaliplatin. J Investig Allergol Clin Immunol 2006; 16(5): 327-30.
4. Gammon D, Bhargava P, McCormick MJ. Hypersensitivity reactions to oxaliplatin and the application of a desensitization protocol. The Oncologist 2004; 9(5): 546-549.
5. Castells M, del Carmen Sancho-Serra M, Simarro M. Hypersensitivity to antineoplastic agents: mechanisms and treatment with rapid desensitization. Cancer Immunol Immunother 2012; 61(9): 1575-84.
6. Gastaminza G, Borbolla J, Goikoetxea MJ, Escudero R, Antón J, Espinos J, et al. A new rapid desensitization protocol for chemotherapy agents. J Investig Allergol Clin Immunol 2011; 21(2): 108-112.
7. Caiado J, Picard M. Diagnostic tools for hypersensitivity to platinum drugs and taxanes: skin testing, specific IgE, and mast cell/basophil mediators. Curr Allergy Asthma Rep 2014; 14(8): 451.
8. Sanchez-Gonzalez M, Mohedano E, Seoane E, Mhanna H, Jimenez A, Fernandez C, et al. Adverse reactions to platinum salts and taxanes: successful desensitization protocols. J Allergy Clin Immunol 2010; 125(2): AB154.

9. Navo M, Kunthur A, Badell ML, Coffer II LW, Markman M, Brown J, et al. Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. Gynecol Oncol 2006; 103(2): 608-13.
10. Zanotti K, Rybicki L, Kennedy A, Belinson J, Webster K, Kulp B, et al. Carboplatin skin testing: a skin-testing protocol for predicting hypersensitivity to carboplatin chemotherapy. J Clin Oncol 2001; 19(12): 3126-3129.
11. Polyzos A, Tsavaris N, Kosmas C, Arnaouti T, Kalahanis N, Tsigris C, et al. Hypersensitivity reactions to carboplatin administration are common but not always severe: a 10-year experience. Oncology 2001; 61(2): 129-33.
12. Koren C, Yerushalmi R, Katz A, Malik H, Sulkes A, Fenig E, et al. Hypersensitivity reaction to cisplatin during chemoradiation therapy for gynecologic malignancy. Am J Clin Oncol 2002; 25(6): 625-626.
13. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J, et al. Paclitaxel-associated hypersensitivity reactions: experience of the gynecologic oncology program of the Cleveland Clinic Cancer Center. J Clin Oncol 2000; 18(1): 102-105.
14. Sliesoraitis S, Chikhale P. Carboplatin hypersensitivity. Int J Gynecol Cancer 2005; 15(1): 13-18.
15. Pagani M. The complex clinical picture of presumably allergic side effects to cytostatic drugs: symptoms, pathomechanism, reexposure, and desensitization. Med Clin North Am. 2010; 94(4): 835-52.
16. Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-Monteagudo R, Guillen-Ponce C, Pueyo C, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. Allergy 2013; 68(7): 853-861.
17. Urquhart LM. Taxanes as a first-line systemic treatment in metastatic breast cancer. Clin J Oncol Nurs 2013; 17: S15-S21.
18. Capriotti K, Capriotti J, Lessin S, Wu S, Goldfarb S, Belum V, et al. The risk of nail changes with taxane chemotherapy: a systematic review of the literature and meta-analysis. Br J Dermatol 2015; 173(3): 842-845.
19. Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, et al. Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. J Allergy Clin Immunol 2007; 119(3): 726-30.
20. Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, costs, and efficacy of rapid drug desensitizations to chemotherapy and monoclonal antibodies. J Allergy Clin Immunol Prac 2016; 4(3): 497-504.
21. Lee C-W, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. Gynecol Oncol 2005; 99(2): 393-399.
22. Hong DI-C. desensitization for Allergic reactions to chemotherapy. Yonsei Med J 2019; 60(2): 119-125.
23. Giavina-Bianchi P, Aun MV, Galvão VR, Castells M. Rapid desensitization in immediate hypersensitivity reaction to drugs. Curr Treat Options Allergy 2015; 2(3): 268-285.
24. Liu A, Fanning L, Chong H, Fernandez J, Sloane D, Sancho-Serra M, et al. Desensitization regimens for drug allergy: state of the art in the 21st century. Clin Exp Allergy 2011; 41(12): 1679-1689.
25. Wu LC. Immunoglobulin E receptor signaling and asthma. J Biol Chem 2011; 286(38): 32891-7.
26. Syrigou E, Triantafyllou O, Makrilia N, Kaklamanos I, Kotanidou A, Manolopoulos L, et al. Acute hypersensitivity reactions to chemotherapy agents: an overview. Inflamm Allergy Drug Targets 2010; 9(3): 206-213.
27. Feldweg AM, Lee C-W, Matulonis UA, Castells M. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. Gynecol Oncol 2005; 96(3): 824-829
28. Boulanger J, Boursiquot J, Cournoyer G, Lemieux J, Masse M, Almanric K, et al. Management of hypersensitivity to platinum-and taxane-based chemotherapy: cepo review and clinical recommendations. Curr Oncol 2014; 21(4): e630-641.
29. Lenz H-J. Management and preparedness for infusion and hypersensitivity reactions. Oncologist 2007; 12(5): 601-609.
30. O'Cearbhaill R, Zhou Q, Iasonos A, Hensley ML, Tew WP, Aghajanian C, et al. The prophylactic conversion to an extended infusion schedule and use of premedication to prevent hypersensitivity reactions in ovarian cancer patients during carboplatin retreatment. Gynecol Oncol 2010; 116(3): 326-331.
31. Williams C, Bryant A. Short versus long duration infusions of paclitaxel for any advanced adenocarcinoma. Cochrane Database of Syst Rev 2011(5): CD003911.
32. Kintzel PE. Prophylaxis for paclitaxel hypersensitivity reactions. Ann Pharmacother 2001; 35(9): 1114-1117.
33. Desai NP, Trieu V, Hwang LY, Wu R, Soon-Shiong P, Gradishar WJ. Improved effectiveness of nanoparticle albumin-bound (nab) paclitaxel versus polysorbate-based docetaxel in multiple xenografts as a function of HER2 and SPARC status. Anticancer Drugs 2008; 19(9): 899-909.
34. Semb KA, Aamdal S, Oian P. Capillary protein leak syndrome appears to explain fluid retention in cancer patients who receive docetaxel treatment. J Clin Oncol 1998; 16(10): 3426-3432.
35. Robinson JB, Singh D, Bodurka-Bevers DC, Wharton JT, Gershenson DM, Wolf JK. Hypersensitivity reactions and the utility of oral and intravenous desensitization in patients with gynecologic malignancies. Gynecol Oncol 2001; 82(3): 550-558.
36. Cernadas J, Brockow K, Romano A, Aberer W, Torres M, Bircher A, et al. General considerations on rapid desensitization for drug hypersensitivity–a consensus statement. Allergy 2010; 65(11): 1357-1366.
37. Del Carmen Sancho M, Breslow R, Sloane D, Castells M. Desensitization for hypersensitivity reactions to medications. Chem Immunol Allergy 2012; 97: 217-233.
38. Limsuwan T, Castells MC. Outcomes and safety of rapid desensitization for chemotherapy hypersensitivity. Expert Opin Drug Saf 2010; 9(1): 39-53.
39. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008; 122(3): 574-580.
40. Confino-Cohen R, Fishman A, Altaras M, Goldberg A. Successful carboplatin desensitization in patients with proven carboplatin allergy. Cancer 2005; 104(3): 640-643.

.....