

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

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### 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 developed 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.

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### 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.<sup>1</sup> Chemotherapeutic agents form an extensive range of drugs just as taxanes, methotrexate, etoposide, and platinum agents (Platins) used for cancer treatment.<sup>2</sup> 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.<sup>3</sup> 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.<sup>4</sup> 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.<sup>5</sup> 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.<sup>6</sup> To reduce HRs, different desensitization protocols formed vary upon physician understandings.<sup>7</sup> In the current review, it was aimed to form literature, indicating available desensitization protocols.

### 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%.<sup>8</sup> 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.<sup>9</sup> 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%.<sup>10</sup> 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.<sup>11</sup>

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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%.<sup>12</sup>

Paclitaxel is used mainly for lung, breast, and gynecological 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%.<sup>13</sup>

### **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.<sup>14</sup> After the 6<sup>th</sup> cycle of exposure to platins, the danger of anaphylaxis elevates and persists to elevate up to the 8<sup>th</sup> cycle as the cumulative risk reaches 19.5%.<sup>15</sup> 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.<sup>16</sup>

### **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.<sup>17</sup> 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.<sup>18</sup>

### **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.<sup>19</sup> 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.<sup>20</sup> Protocols for desensitization characteristically involves the stepwise increase in the administration of allergen medicine with no life-threatening symptoms.<sup>21</sup>

### **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.<sup>22</sup> 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.<sup>23</sup> 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.<sup>24</sup>

As RDD leads to temporary insensitivity, patients require to be desensitized before every exposure with the culprit medication.<sup>25</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>28</sup>

### **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.<sup>29</sup> 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%.<sup>30</sup> 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.<sup>31</sup>

### 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.<sup>32</sup> 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 before treatment.<sup>33</sup> A simple regimen of premedication comprising of only one IV or oral steroid dose (10 mg), given half-hour before paclitaxel administration.<sup>13</sup> 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 before administration.<sup>34</sup>

### Desensitization protocol of Platins and Taxanes

Various protocols for desensitization have been effectively used to handle HSRs to taxanes and platinum-containing compounds.<sup>35</sup> 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.<sup>36</sup> 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.<sup>37</sup> The 12-step desensitization protocol was designed by the Dana-Farber Cancer Institute and the Brigham and Women's Hospital.<sup>38</sup> 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.<sup>27</sup>

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.<sup>38, 39</sup>

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.<sup>40</sup> 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.<sup>4</sup>

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 desensitizations 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 rate<sup>27</sup>.

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 hypotension, 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.<sup>39</sup>

## 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.

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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.

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