Clinics in Oncology

Research Article
Published: 23 Mar, 2024

Castell's Rapid Desensitization as a Major Therapeutic Opportunity for Patients Experiencing Hypersensitivity Reactions to Antiblastic Drugs

Calabrò C, Carofiglio F, Ferraiuolo S, Laforgia M, Vincenti A, Ungaro V and Nardulli P*

Giovanni Paolo II/I.R.C.C.S. Cancer Institute, Italy

Abstract

The expanding use of conventional and new chemotherapy agents in a wide variety of malignancies is increasing the incidence rate of Hypersensitivity Reactions (HSRs); skin rashes, itching, temperature, chills, localized face redness, dizziness, headache, dyspnea, anxiety and, in some severe cases, chest pain, bronchospasm, and anaphylaxis are the major clinical events of HSRs [1].

The above-mentioned signs can occur even after adequate premedication with antihistamine and corticosteroid drugs, therefore precluding the treatment itself, depriving the patient of a great chance of treatment and recovery.

In this analysis, a cohort of 48 patients have been monitored since October 2022 until October 2023 in order to observe and report all the rapid desensitization procedures they underwent over the period considered, according to Castells' protocol.

The aim of this paper is to describe the experience of an Italian cancer hospital with Castell's rapid desensitization protocols in patients with a previous medical history for Drug Hypersensitivity Reactions (DHRs), proving that the desensitization protocol is feasible and safe without compromising cytotoxic activity.

Introduction

Drug hypersensitivity

Drug Hypersensitivity (DH) is an immune-mediated reaction to drugs, an issue which oncologists are currently grappling with.

Particularly, DHRs related to antineoplastic drugs represent a huge problem due both to the unavailability of diagnostic methodologies to predict DHs and to the shortage of alternative treatment options.

Biomarkers of DHRs include tryptase, histamine, leukotrienes, and prostaglandins in type I reactions and IL- 6, TNF-α, and IL-1β in cytokine release or mixed reactions.

Considering that HDRs represents the cause of 3% to 6% of hospital admissions and occur in 10% to 15% of hospitalized subjects [2], it seems to be reasonable to fix the problem with either drug discontinuation, or supportive treatment (antihistamines, corticosteroids, epinephrine) or desensitization.

DHRs, as expected, are often related to the administration of monoclonal antibodies but also taxanes and platinum derivatives show the same trend. The mechanisms underlying these reactions are not fully understood, but include both IgE-mediated and non-IgE-mediated reactions.

In details, it can be assumed by phenotypes of platin HRs that they include type I reactions, cytokine release reactions, and mixed reactions, with the most heterogeneity seen with oxaliplatin which can trigger cytokine release reactions presenting with fevers, chills, rigors, headache, chest pain, and/or back pain along with elevated levels of IL-6 and TNF-α [3]. In contrast to carboplatin and cisplatin, cases of immune-mediated hemolytic anemia and thrombocytopenia complicated by bleeding have also been reported for oxaliplatin [4]. On the other hand, taxanes may cause mast cell and/or basophil activation through IgE-mediated mechanisms, direct action on basophils, or IgG-mediated mechanisms that cause complement activation and release of anaphylatoxins (C3a, C5a). Taxanes contain, in their commercial formulation, emulsifying agents (polyethoxylated castor

OPEN ACCESS

Correspondence:
Concetta Calabrò, Giovanni Paolo II/ I.R.C.C.S. Cancer Institute, Italy

Received Date: *22 Feb 2024*
Accepted Date: *18 Mar 2024*
Published Date: *23 Mar 2024*

Citation:
Calabrò C, Carofiglio F, Ferraiuolo S, Laforgia M, Vincenti A, Ungaro V, et al. Castell's Rapid Desensitization as a Major Therapeutic Opportunity for Patients Experiencing Hypersensitivity Reactions to Antiblastic Drugs. Clin Oncol. 2024; 9: 2063.

ISSN: 2474-1663

oil for paclitaxel and polysorbate 80 for docetaxel and cabazitaxel), capable to activate mast cells through an IgE-mediated mechanism or direct complement activation with the consequent release of anaphylatoxins [5].

The incidence of HRs to paclitaxel and carboplatin has been evaluated in gynecological cancer, especially in cases of ovarian cancer, at rates of 8% to 16% [6,7].

Correlations between viral infections and DHRs have been also known. Examples are the frequency of Maculopapular Exanthema (MPE) to ampicillin/amoxicillin during EBV infection, the increased prevalence of reactions to Trimethoprim-Sulfamethoxazole (TMP-SMX) in patients with HIV infection, the association between from HHV-6 and allergy to anticonvulsants [8].

The mechanisms by which viral infection promotes drug hypersensitivity are numerous and still poorly understood. It has been hypothesized that any delayed-type immune drug response can occur only in the presence of danger signals deriving from a stress condition (chemical, physical or viral) [9].

Overall, reactions to drugs are divided into immediate and delayed. The immediate reactions occur within 1 h after the drug intake and are mostly associated with an IgE-mediated or pseudo-allergic pathogenic mechanism. Delayed reactions occur more than 6 h after the last drug intake, usually 2 to 5 days, and are cell-mediated. Between 1 and 6 h, immediate reactions may still occur.

The onset timing of DHRs is variable and related to the medications administered for chemotherapy. Allergic reactions to platinum derivatives typically arise after several infusion cycles; more than 27% of patients receiving at least 7 cycles of carboplatin have reactions, and half of those are moderate to severe [10], while about 95% of immediate reactions to taxanes occur during the first or second administration [11-13], within a few minutes following the start of the infusion, resulting in their promptly resolution after the infusion is stopped. Approximately 16% to 40% of patient receiving paclitaxel experience DHRs on first exposure to this drug, although the use of premedication decreased this rate to less than 10% [5].

In accordance with AIOM guidelines about emergencies and urgencies in oncology, platinum salts may cause most frequently acute reactions with prolonged exposure, and in 5% of cases the reaction takes place during the second cycle of therapy. As a single agent, the monoclonal antibody rituximab causes most DHRs (27%), followed by paclitaxel (10%). About half of all hypersensitivity reactions are due to monoclonal antibodies, and in 54% of cases to rituximab. Symptoms of acute reactions are immediate, within a few minutes from the start of the infusion, while moderate reactions usually occur hours or days after infusion. In more than half of cases, patients experience the following symptoms: Chest pain, dyspnea, and exanthema for taxanes, dyspnea and exanthema for platinum salts and chills and stiffness for monoclonal antibodies. In details, for oxaliplatin the HRs risk increases with cumulative dose (>5 cycles), for cisplatin the reaction occurs after few minutes from the start of the infusion, for carboplatin HRs seem to be quite moderate-severe, for both paclitaxel and docetaxel reactions are generally related to solvents in pharmaceutical preparation [14]. In the latter case, the HRs depend on the dose and the rate of infusion, occur up to 30% of cases and reduced to 4% using premedication with corticosteroids and antihistamines [15]. Reactions associated with monoclonal antibodies also occur during the first administration with a cytokine-mediated mechanism and the symptoms seem to decrease at subsequent administrations; symptoms caused by cytokines release can be mitigated by immediate suspension of infusion, antihistamines administration and slowing of infusion rate. Rituximab and trastuzumab are the monoclonal antibodies most associated with cytokine release syndrome (77% and 40% at first administration, respectively) but they rarely lead to discontinuation of treatment [16]. Most of monoclonal antibodies, with the exception of bevacizumab and panitumumab, require premedication with paracetamol and antihistamines.

Rapid desensitization

When a HR to platinum agents or taxanes occurs, it is often necessary to suspend the administration of the drug even permanently, because any effort in decreasing its rate by administering premedication or slowing down the infusion rate seems to be ineffective. Moreover, switching to different drugs of the same class (e.g. carboplatin and cisplatin, paclitaxel and docetaxel) is not always recommended due to high risk of cross-reactivity.

Thus, rapid desensitization can be performed when replacing the drugs responsible for HRs with less effective chemotherapy is required or in case of irreplaceability of those drugs or severe disease, in order to ensure personalized care with target dose of medication in divided incremental steps.

Rapid drug desensitization was introduced in clinical practice in the 2000s for the first time, becoming the standard of care for patients with platinum and taxane agent HRs [5]. The rapid desensitization is based on the same principles of the desensitization to the hymenopteran venom; the main difference between the two procedures is their duration in time; the first one lasts 3 h, the second one 3 months.

This procedure consists in injecting gradually increasing doses of the drug at 15-min intervals, starting from a very low dilution (1/50.000) of the target dose. Once the maximum dose is reached, the subject is desensitized so he can perform the whole therapy.

In details, the most widely accepted desensitization protocol for platinum agents and taxanes is a 12-step protocol using 3 dilutions (1:100, 1:10, 1:1) with a 2- to 2.5-fold increase between consecutive steps based on in vitro mechanisms of mast cell IgE desensitization [17]. This is the successful 6-h, 3-bags, 12-steps carboplatin desensitization protocol originally reported in gynecologic oncology patients with the first series of 10 patients who underwent 35 desensitization procedures, of which 31 (89%) were completed without reaction and the remaining 4 involved mild cutaneous reactions that did not prevent completion [18].

During the first 11 steps of the procedure, the drug concentration grows in a hyperbolic way, ensuring tolerance to drug administration; in contrast, during the last twelfth step, the drug concentration remains constant.

Similar rapid (2-bag, 8-step), intermediate (3-bag, 12-step), and prolonged (4-bag, 16-step) desensitization protocols have been published for taxanes [19].

The successful use of a 12-step desensitization for paclitaxel and docetaxel was first published in a series of 17 gynecologic oncology patients who underwent 77 desensitization procedures [20].

Premedication can vary significantly between desensitization

protocols, but there are limited data available on optimal premedication regimens. They may incorporate H1 antihistamines, H2 blockers, steroids, montelukast, and/or aspirin and other COX-1 inhibitors.

The aim of rapid desensitization is to induce a temporary tolerance, that is, during the period in which the patient is exposed to the antigen (drug). If the patient spends 24 h to 48 h without exposure to the antigen, sensitization will occur, making the patient vulnerable again if exposed.

The mechanisms underlying this procedure include a number of cellular machineries:

- Ion channels coupled receptors undergo a conformational change resulting in strong bonds between agonist molecules and receptors, without opening the ion channel;
- Gradual reduction of receptor density due to their internalization by endocytosis;
- Depletion of intermediate mediators from the vesicles of the neuronal terminal;
- Homeostatic response leading to physiological adaptation.

The procedure of rapid desensitization owes its effectiveness to its capability to maintain a constant serum drug concentration. Hypersensitivity usually recurs within 24 h to 48 h after stopping treatment. Minor reactions (e.g., pruritus, rash) are common during desensitization.

This procedure is not recommended in patients who have experienced Stevens-Johnson syndrome, serum sickness, drug rash with eosinophilia and systemic symptoms, or other severe delayed or cutaneous hypersensitivity reactions.

Desensitization is usually not effective for T-cell-mediated reactions, and should not be performed in these cases. Whenever desensitization is performed, oxygen, adrenaline, and resuscitation equipment should be available so that an anaphylactic reaction can be readily addressed.

Materials and Methods

Our study regards a cohort of patients receiving several rapid desensitization procedures on average performed between October 2022 and October 2023. Cyclophosphamide, paclitaxel, docetaxel, PEGylated liposomal doxorubicin hydrochloride, carboplatin, oxaliplatin, and cabazitaxel: these were the drugs involved in the desensitizing procedures that were performed according to AIOM line guide about emergencies and urgencies in oncology cited above, and to Hospital protocol. All 46 patients underwent the most used and validated method of desensitization, described by Castells et al. [8], applied for the desensitization of several antineoplastic drugs, including platinum compounds. The Castells protocol requires, for its proper success, the close collaboration between oncologist, allergist and pharmacist, in order to provide the best possible treatment for each patient.

This collaboration leads to all the activities that make up the complex procedure of desensitization, as mentioned in the hospital validated protocol.

First of all, just according to that protocol, the patients who have experienced a certified HR to antiblastic drugs need to be discussed during a multidisciplinary team in order to assess the clinical suitability of patient to the start of the procedure. In details, the oncologist presents the case to the resuscitator, to the cardiologist, to the pharmacist and to the dedicated nurses within 72 h from patient identification. At the outcome of the evaluation, the patient is informed about the ways and times of the procedure and, at the end of the interview, he signs the ICF (informed consent form) at the presence of both oncologist and allergist. The patient can revoke the ICF whenever he wants, for any reason. Once consent has been obtained from the patient, the allergist plans the desensitization scheme in accordance to the oncologist, then send it to the chemotherapy manipulation unit by a computerized prescription system (UMaCA). The prescription scheme contains all the information in order to identify the patient, his diagnosis and therapy. The hospital pharmacist has the task of checking and validating the prescription so that the chemotherapy bag can be prepared and dispensed. This step is essential to intercept and avoid any dosing and drug concentration errors. Furthermore, it is important to remember that, during the preparation phase of the drug bags, the pharmacist has always checked the concentration and stability limits for each drug according to the technical data sheet. For example, in the case of carboplatin, the mother solution, was prepared respecting the lower limit concentration of 0.5 mg/ml. At this point, the chemotherapy bags are carried to the administration room where the desensitization procedure is performed in the presence of the allergist and the dedicated nurses. Before, during and after the desensitization procedure the nurses monitor the clinical conditions of the patient by evaluation of his vital signs. In case of a severe DHR during a desensitization procedure, the nurses have to inform the anesthetist-resuscitator for the management of respiratory symptoms including bronchospasm, cough and wheezing. The infusion is performed by electronic infusion pumps with an alarm system for patient safety.

In our experience, we registered 238 rapid desensitization procedures, with a total of 46 patients monitored, 40 of which were women; 2 patients were desensitized to PEGylated liposomal doxorubicin, 8 to carboplatin, 1 to cyclophosphamide, 3 to docetaxel, 8 to oxaliplatin and 27 to paclitaxel. Three patients received two different drugs with desensitization protocol.

The desensitization procedure provides for the administration of three or four solution with different drug concentration respectively in 12 or 20 different steps within one day, varying the rate of infusion every 15 min.

In details, some more critical cases characterized by increased risk of experiencing DHRs required the physicians to choose the 20-step protocol instead of the 12-step protocol.

Desensitization procedure steps

In the 20-step protocol, solution 1 is a 1000-fold dilution of the final target concentration; solution 2 is a 100- fold dilution of the final target concentration; solution 3 is a 10-fold dilution of the final target concentration, and the concentration of solution 4, called mother solution, is calculated by subtracting the cumulative dose administered in steps 1 to 19 from the total target dose and dividing by the bag volume, as shown in the table below. In the 12-step protocol, the greater dilution is 100-fold of the mother solution.

According to this method, because many of the solutions are not completely infused, the total volume and dose calculated are more than the final dose and volume given to the patient.

The desensitization procedure requires for its administration from 6 h to 8 h during which the patient must be carefully monitored by dedicated nurses, the oncologist and the allergist.

For each patient, we collected information about the drug administered and dosage reductions planned by the oncologist due to hypersensitivity phenomena; total number of cycles per patient actually administered compared to the number established by the oncologist.

The desensitization protocol implemented foresees the involvement of nurses specialized in antiblastic chemotherapy manipulation and administration, operating under a pharmacist supervision. The infusion bags must be prepared under a laminar vertical flow hood with High Efficiency Particulate Air filter (HEPA) class IIA in order to ensure the sterility of the prepared solution and protect the operator from antiblastic contaminations. For this reason, the nurses must wear all necessary protective equipment such as gloves, lab coat, bonnet, face mask, non-perforated footwear and have the anti-spill kit always available in the laboratory, a negative pressure room separated by locking doors from other workrooms. For the setting up of infusion bags, Closed System Drug-Transfer Device (CSTD) are used. In order, the nurse pierces the elastomeric membrane of the drug vial with a vial adapter (protector) equipped with a small balloon to equalize the vial pressure, then, with a Luer-lock syringe equipped with its adapter, he draws up the correct amount of concentrate for solution for infusion drug and infuses it into a 0.9% saline bag or 5% glucose solution for its dilution, it depends on the drug compatibility with used diluents. The volumes of medication to be taken and of saline solution to be used shall be calculated on the basis of the dosage regimen given in the data sheet. Eventually, when the data sheet requires it, the dedicated nurses add a 0.22 μm filter to the bags.

As opposed to administration, the preparation of desensitization infusion bags starts from the mother solution. It consists of a bag of saline or glucose solution in which a certain amount of medication is diluted, so that the final volume is given by the sum of the diluent and the volume of medication added. To follow, the 1/10 dilution infusion bag is prepared drawing up into a syringe 10 mL of mother solution then diluting them in 90 mL bag of saline (10 ml are removed from a 100 mL saline bag) or glucose solution. Lastly, the 1/100 dilution infusion bag is prepared drawing up into a syringe 10 mL of 1/10 previously dilution. The 10 mL of 1/10 solution are diluted in 90 mL bag of saline (10 ml are removed from a 100 mL saline bag) or glucose solution. Once the drug bag preparation is completed, the pharmacist performs the visual final inspection in order to identify precipitated particles. In this case, the bag is thrown away. To identify with precision the used drug vials, we have register indicating their batch and expiration date is used.

Results and Discussion

In our retrospective analysis we considered 238 desensitization procedures, performed between October 2022 and October 2023. Considering all the patients analyzed and the two different possible desensitization schemes (20 steps or 12 steps protocol), 806 bags have been prepared in total.

Of the 46 patients considered, only 8 received the 20-step-protocol.

The medium administered dose of paclitaxel was 170 mg (the lowest dose 70 mg and the higher dose 330 mg), that of oxaliplatin was 130 mg (the lowest dose 35 mg and the higher dose 160 mg), that of carboplatin was 370 mg (the lowest 210 mg and the higher 500 mg), that of PEGylated liposomal doxorubicin was 60 mg (the lowest dose 45 mg and the higher dose 78 mg), and finally, that of docetaxel was 115 mg (the lowest dose 85 mg and the highest dose 135 mg).

The data obtained showed that 77% of all treated and analyzed patients (about 35 people) actually received 100% of the expected dose based on the treatment schedule chosen by the oncologist. Only 1 patient (2%) received a dose reduction to 90% of the total dosage, another one (2%) performed the procedure receiving the 80% of the total dosage. The 8.3% of patients experienced a 75% dosage, while 2% received the 70% of total dosage. The lowest reduction was 50% of total dosage, experienced by a single patient (2%).

The remaining 6.7% of patients experienced an extremely personalized dosage of desensitization procedure, according to the advanced age or the presence of comorbidity that forced the oncologist not to administer the data sheet dosage. In these cases, it was not possible to define a point dosage reduction just because this was not directly related to the chance of experiencing a DHR.

It's important to underline that all the dosage reductions mentioned above are not related to drug hypersensitivity but to different ADR (Adverse Drug Reaction) such as neutropenia, hepatic disorders, etc.

Of 46 patients mentioned above, 27 (58% of them) completed entirely the cycles expected for their diagnosis and prescribed by the oncologist during the analyzed period.

As a result of the analysis carried out, the administration of the whole number of cycles estimated for each patient is a success of the application of the desensitization scheme.

Considering the short period analyzed and the limited sample size, we cannot determine whether the results obtained are statistically significant.

However, we may affirm that the illustrated results are very promising, but they need a further proof in a systematic prospective trial capable of overcome the limits of this paper, such as the observed sample size, the hypersensitivity grades of each patient enrolled, the deep knowledge about each diagnosis and stage of disease. Moreover, it is necessary to extensively investigate the desensitization failure related to the clinical condition of each patient.

Basing on the therapeutic results described in this paper, reviewed considering the available scientific literature, the desensitization according to Castell's protocol can be considered safe and useful in order to provide the best therapeutic option for each patient, relying on the very close cooperation between the oncologist, the allergist, and the pharmacist; each of them, in fact, makes a fundamental contribution to the success of the procedure, thanks to their vast experience and complementary skills.

In the end, the observed results show that this therapeutic strategy is a reasonable choice in case of lack of different equally effective therapeutic options, and potentially avoids pharmaceutical regimen interruption, providing the best pharmacological treatment for patients otherwise forced to migrate to other therapeutic approaches.

References

1. Roselló S, Blasco I, Fabregat LG, Cervantes A, Jordan K; ESMO Guidelines Committee. Management of infusion reactions to systemic anticancer

therapy: ESMO Clinical Practice Guidelines. Ann Oncol. 2017;28(Suppl 4):iv100-18.

2. Thong BY, Tan TC. Epidemiology and risk factors for drug allergy. Br J Clin Pharmacol. 2011;71(5):684-700.
3. Silver J, Garcia-Neuer M, Lynch DM, Pasaoglu G, Sloane DE, Castells M. Endophenotyping oxaliplatin hypersensitivity: Personalizing desensitization to the atypical platin. J Allergy Clin Immunol Pract. 2020;8:1668-80.e2.
4. Wong JT, Ling M, Patil S, Banerji A, Long A. Oxaliplatin hypersensitivity: Evaluation, implications of skin testing, and desensitization. J Allergy Clin Immunol Pract. 2014;2(1):40-5.
5. Tsao LR, Young FD, Otani IM, Castells MC. Hypersensitivity reactions to platinum agents and taxanes. Clin Rev Allergy Immunol. 2022;62(3):432-48.
6. Koshiba H, Hosokawa K, Kubo A, Miyagi Y, Oda T, Miyagi Y, et al. Incidence of carboplatin-related hypersensitivity reactions in Japanese patients with gynecologic malignancies. Int J Gynecol Cancer. 2009;19(3):460-5.
7. Markman M, Kennedy A, Webster K, Kulp B, Peterson G, Belinson J. Paclitaxel-associated hypersensitivity reactions: Experience of the gynecological oncology program of the Cleveland Clinic Cancer Center. J Clin Oncol. 2000;18(1):102-5.
8. 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):574-80.
9. Sullivan J, Shear N. The drug hypersensitivity syndrome. What is the pathogenesis? Arch Dermatol. 2001;137(3):357-64.
10. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, et al. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol. 1999;17(4):1141.
11. Castells M. Desensitization for drug allergy. Curr Opin Allergy Clin Immunol. 2006;6(6):476-81.
12. Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, et al. Hypersensitivity reactions related to oxaliplatin (OHP). Br J Cancer. 2003;89(3):477-81.
13. Peereboom DM, Donehower RC, Eisenhauer EA, McGuire WP, Onetto N, Hubbard JL, et al. Successful re-treatment with taxol after major hypersensitivity reactions. J Clin Oncol. 1993;11(5):885-90.
14. Makrilia N, Syrigou E, Kaklamanos I, Manolopoulos L, Saif MW. Hypersensitivity reactions associated with platinum antineoplastic agents: A systematic review. Met Based Drugs. 2010;2010:207084.
15. Joerger M. Prevention and handling of acute allergic and infusion reactions in oncology. Ann Oncol. 2012:23(Suppl 10):x313-9.
16. Bupathi M, Hajjar J, Bean S, Fu S, Hong D, Karp D, et al. Incidence of infusion reactions to anti-neoplastic agents in early phase clinical trials: The MD Anderson Cancer Center experience. Invest New Drugs. 2017;35(1):59-67.
17. Morales AR, Shah N, Castells M. Antigen-IgE desensitization in signal transducer and activator of transcription 6-deficient mast cells by suboptimal doses of antigen. Ann Allergy Asthma Immunol. 2005;94(5):575-80.
18. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: A 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecol Oncol. 2004;95:370-6.
19. Otani IM, Lax T, Long AA, Slawski BR, Camargo CA, Banerji A. Utility of risk stratification for paclitaxel hypersensitivity reactions. J Allergy Clin Immunol Pract. 2018;6(4):1266-73.e2.
20. Feldweg AM, Lee CW, 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):824-9.