

# The role of the allergist in the management of chemotherapy-induced hypersensitivity reactions

ALERGOLOGO VAIDMUO CHEMOTERAPIJOS SUKELTŲ PADIDĖJUSIO JAUTRUMO REAKCIJŲ VALDYME

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**Summary.** Chemotherapy-Induced Hypersensitivity Reactions are one of the main problems for oncology physicians and chemotherapy patients. The hypersensitivity reaction can either cause the cessation of the first-line treatment and it may impair the final result and impede or decrease the chances for successful treatment. Chemotherapy drugs are foreign substances that are capable to inducing the various hypersensitivity reactions from mild cutaneous symptoms to severe respiratory distress and cardiovascular collapse. The original Gell and Coomb's classification categorizes hypersensitivity reactions into four types according to the type of immune response and the effector mechanism responsible for cell and tissue injury. The most common reactions are caused by platinum compounds, taxanes, epipodophyllotoxins, and asparaginase. The use of biologicals is increasing now, and these drugs are frequent causes of hypersensitivity reactions too. Skin testing is a method of diagnosing drug hypersensitivity, but it has not been developed enough in the field of medical oncology where a variety of the antineoplastic agents may be caused hypersensitivity reactions. Drug desensitization is the beneficial therapy in patients with chemotherapy-induced hypersensitivity reactions to chemotherapeutic drugs. This is useful for chemotherapy patients with malignancies and hematological diseases when no comparable alternative is available.

**Keywords:** chemotherapy-induced hypersensitivity reactions, skin testing, drug desensitization.

**Santrauka.** Chemoterapijoje vartojamų vaistų sukeltos padidėjusio jautrumo reakcijos yra viena pagrindinių problemų, su kuria susiduria gydytojai onkologai ir piktybinėmis ligomis sergantys pacientai. Išryškėjus padidėjusio jautrumo reakcijoms į medikamentus, skirtus gydyti onkologines ligas, neretai nutraukiamas pirmosios eilės vaistinių preparatų skyrimas, o tai gali sumažinti sėkmingo gydymo galimybes. Padidėjusio jautrumo reakcijos gali pasireikšti nuo lengvų odos simptomų iki sunkių kvėpavimo, širdies ir kraujagyslių sistemos simptomų (pvz., anafilaksinio šoko). Gell ir Coombs klasifikacijoje padidėjusio jautrumo reakcijos suskirstytos į keturis tipus pagal imuninio atsako tipą ir mechanizmą, atsakingą už ląstelių ir audinių pažeidimus. Dažniausiai reakcijas sukelia platinos junginiai, taksanai, epipodofilotoksinai ir asparaginazė. Didėja biologinių vaistų, kurie taip pat laikomi dažna padidėjusio jautrumo reakcijų priežastimi, vartojimas onkologijoje. Klinikinėje praktikoje lengva atlikti alerginius odos mėginius, siekiant diagnozuoti įsijautrinimą onkologinėms ligoms gydyti skirtiems vaistams, tačiau šie tyrimai vis dar nėra dažnai atliekami. Desensibilizacija – tai procesas, kurio metu keičiamas imuninis atsakas į vaistą ir sukeliamą laikina tolerancija. Šis gydymo metodas yra gyvybiškai svarbus, kai nėra alternatyvių gydymo būdų ir (arba) medikamentų.

**Reikšminiai žodžiai:** chemoterapijos sukeltos padidėjusio jautrumo reakcijos, alerginiai odos tyrimai, desensibilizacija vaistams.

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## INTRODUCTION

Chemotherapy drugs are a cornerstone of cancer treatment, used to kill rapidly dividing cancer cells and slow or halt tumor growth. However, their use is frequently accompanied by a range of adverse effects, including nausea, vomiting, fatigue, and hair loss. One of the most concerning of these is hypersensitivity reactions (HSRs), which can occur in response to the administration of chemotherapy drugs.

HSRs are immune-mediated reactions that can range from mild to life-threatening. They can occur immediately, within minutes to hours after drug expo-

sure, or several days after drug administration. HSRs can manifest in a variety of ways, including: skin rash, itching, hives, facial swelling, shortness of breath, chest pain, and anaphylaxis. These reactions may lead to treatment interruption, dose reduction, or even discontinuation of the treatment. On some occasions, it may be lethal because of anaphylaxis.

The mechanisms underlying HSRs are complex and varied, involving multiple components of the immune system, including: antibodies, immune complexes, and T-cells (cytotoxic and natural killers). Understanding the types of HSRs and their clinical manifestations is

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critical for accurate diagnosis and effective management. Moreover, identifying risk factors for HSRs and developing strategies to prevent and control their occurrence is essential for ensuring the safety and efficacy of chemotherapy treatment.

## CLASSIFICATION

HSRs can be classified into four types based on the underlying mechanisms of the immune response this classification system is also referred to as Gell and Coombs classifications (Table 1) [1].

### Type I

Type 1 HSRs involve the activation of B-cells, which produce IgE antibodies in response; to an allergen, including certain chemotherapy drugs. The binding of these IgE antibodies at a specific binding site (FcεRI), on the surface of mast cells and basophils) [2, 3]. This leads to the release of vasoactive inflammatory mediators including: histamine, tryptase, prostaglandins, and leukotrienes, propagating the inflammatory cascade, which in turn gives us the presentation of the HSRs [3].

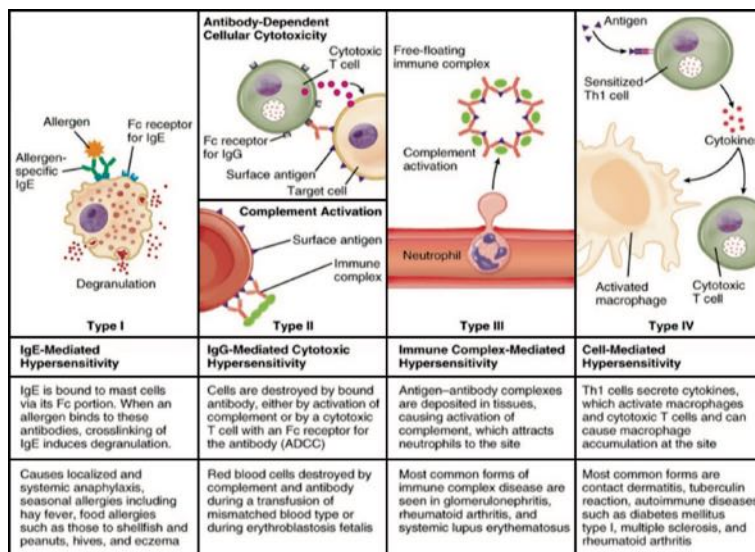
Histamine is a particularly important mediator in type I reactions. It causes vasodilation and increased vascular permeability, leading to edema and swelling. It also stimulates the contraction of smooth muscle in the lungs, causing bronchoconstriction and wheezing. In severe cases, the release of histamine can lead to anaphylaxis, a life-threatening condition that can cause difficulty breathing, a rapid heart rate, and low blood pressure (Table 2) [4].

### Type II

Type II HSRs are mediated by IgG antibodies that recognize and bind to antigens on the surface of cells, including drug-induced antigens. This binding triggers the activation of the complement system, which causes the destruction of the cells by phagocytic cells. In the case of chemotherapy drugs, type II reactions can lead to hemolytic anemia, thrombocytopenia and other blood disorders [4, 5].

### Type III

Type III HSRs to chemotherapy drugs involve the formation of immune complexes, which are composed of drug metabolites or drug-protein complexes that are recognized as foreign by the immune system. The



**Figure 1. Hypersensitivity reactions by Coomb and Gel classification (adopted from Anatomy & Physiology, Connexions Web site. <http://cnx.org/content/col11496/1.6/>, Jun 19, 2013)**

**Table 1. The classification of Coombs and Gell's hypersensitivity reaction type I-IV [1]**

| Hypersensitivity Type     | Mechanism                          | Key factors                           | Timeframe      |
|---------------------------|------------------------------------|---------------------------------------|----------------|
| Type I (Immediate)        | IgE-mediated                       | IgE antibodies, mast cells, basophils | Within minutes |
| Type II (Cytotoxic)       | Antibody-mediated cell destruction | IgG/IgM antibodies, complement system | Variable       |
| Type III (Immune Complex) | Immune complex formation           | IgG antibodies, complement system     | Hours to days  |
| Type IV (Delayed)         | T cell-mediated                    | T cells, macrophages                  | Hours to days  |

**Table 2. Immediate HSRs symptoms to chemotherapy agents (adapted from EAACI Position Paper) [20]**

| Category              | Key Symptoms  |
|-----------------------|---|
| Cardiovascular        | Sensation of faintness, hypotension                 |
| Respiratory           | Dyspnea, cough, wheezing                            |
| Neurological          | Feelings of anxiety, alterations in cognitive state |
| Gynecological         | Pruritus in vaginal region, uterine cramping        |
| Cutaneous and Mucosal | Flushing, appearance of urticaria, angioedema       |
| Craniofacial          | Ocular pruritus, nasal pruritus, tingling of lips   |
| Gastrointestinal      | Nausea, abdominal cramping, diarrhea                |

deposition of these immune complexes in tissues can lead to inflammation and tissue damage, particularly in organs such as the kidneys, lungs, and joints [6].

### Type IV

Type IV HSRs are mediated by T-cells, particularly CD4+ helper T cells. When a drug is introduced into the body, it is processed by antigen-presenting cells, which present drug-specific peptides to CD4+ T-cells. These T-cells become activated and release cytokines that recruit and activate macrophages and other immune cells. The activation of these cells leads

to inflammation and tissue damage, which can manifest as skin rash, blistering, other skin lesions, or as inflammation in the lungs, liver, or other organs [7].

It is important to mention that type IV hypersensitivity is also divided into 4 subclasses:

- IVa involves a Th1 response with monocyte involvement, leading to the release of cytokines such as IFN-gamma, IL-1, and IL-2.
- IVb is characterized by a Th2 response with eosinophil activation, accompanied by cytokines like IL-4, IL-5, and IL-13.
- IVc is associated with a T CD8+ response and the release of cytokines such as perforin, granzyme B, and Fas Ligand.
- IVd entails reactions from both T CD4+ and CD8+ cells, directing neutrophil activity and the release of cytokines like IL8 and granulocyte monocyte colony-stimulating factor (GM-CSF) [8].

### CYTOKINE RELEASE REACTIONS

Cytokine release reactions (CRR) have clinical signs that manifest as a result of cytokine release leading to elevated serum TNF- $\alpha$  and IL-6 levels. CRR do not respond to premedication or slower infusion rate during the first infusion. CRR can occur at first infusion and present with flushing, fever, chills, rigor, headache, back pain, tachycardia, hypertension or hypotension, syncope, nausea, and vomiting. Some of these symptoms overlap with type 1 reactions which tend to occur after repeated exposure [9].

### Infusion-related reactions

Patients mostly suffer from IRR (infusion-related reactions) at the first infusion. IRR (fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headaches, hypotension, hypertension, and flushing) are mediated by cytokine release from monocytes. It is usually affected by the infusion pulse. Clinical picture is similar to Type I HR or CRR, in severity; we observe only mild to moderate levels that will subside gradually with each following infusion, as well as good response to premedication [9].

### Chemotherapy-induced hypersensitivity reactions

Chemotherapeutic drugs have been widely used in the treatment of cancer disease for about 70 years, and the number of therapeutics is increasing. Despite the large number of chemotherapy drugs, hypersensitivity reactions are the most common among platinum compounds (cisplatin, carboplatin), epipodophyllo-

toxins (teniposide, etoposide), asparaginase, taxanes (paclitaxel), and procarbazine. Despite their prevalence and relevance, the ideal pathways for the diagnosis, treatment, and prevention of these reactions are still unclear. Furthermore, biologicals play a pivotal role as targeted therapies in treating cancer, with their usage expanding in clinical settings. As a result, they have become increasingly associated with hypersensitivity reactions (HSRs). Patients may experience HSRs to these medications either upon initial exposure or after multiple treatments, and these reactions can pose severe risks to life or restrict treatment choices.

### Platinum agents

The platinum derivatives cisplatin, carboplatin, and oxaliplatin are approved worldwide as agents in chemotherapy and are used as part of the treatment protocol (Table 3). Platinum derivatives exert their effects; the DNA adducts induce different cellular responses such as transcription inhibition, cell cycle arrest, DNA repair, and apoptosis [11]. HSRs to platinum agents are common, most patients experience mild reactions but the severity can vary and even lead to death [12].

### Taxans

The anti-cancer activity of taxanes lies in their ability to trigger abnormal mitotic spindle formation by stabilizing microtubules, leading to the delay of mitotic progression and finally to cell death (Table 4) [13, 14]. However, the use of taxanes is not without its risks. During clinical therapy, we can expect the fol-

**Table 3. Platinum agents and basic description of the mechanism of work [10]**

| Platinum Agent | Mechanism of Action  |
|----------------|--|
| Cisplatin      | Forms intrastrand and interstrand DNA crosslinks by binding to purine bases, leading to DNA damage and apoptosis.          |
| Carboplatin    | Similar to cisplatin, forms DNA crosslinks, but with a different spectrum of activity and reduced toxicity.                |
| Oxaliplatin    | Induces DNA damage by forming intrastrand crosslinks, particularly with guanine bases. Also interferes with RNA synthesis. |

**Table 4. Taxane family agents and their respective mechanisms [13]**

| Taxane Chemotherapy Agent | Mechanism of Action   |
|---------------------------|---|
| Paclitaxel                | stabilizes microtubules, preventing their depolymerization. This leads to the inhibition of mitosis and cell division, ultimately causing cell death.   |
| Docetaxel                 | promotes the assembly of microtubules and inhibits their disassembly, leading to the stabilization of microtubules. This disruption of normal microtubule function results in cell cycle arrest and inhibition of cell proliferation.       |
| Cabazitaxel               | it is a semi-synthetic taxane derivative, which inhibits microtubule depolymerization. This action leads to cell cycle arrest and apoptosis, making it effective in the treatment of prostate cancer that is resistant to other treatments. |

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**Table 5. Comparison between hypersensitivity testing methods [25–30]**

| Test                 | Duration      | Procedure                                      | Interpretation   | Types of Reactions Evaluated                                     |         |
|----------------------|---------------|--|--|--|---------|
| Skin Prick Test      | 15–20 minutes | Small amount of allergen pricked into the skin | Size of wheal (bump) and flare (redness) measured          | Immediate hypersensitivity reactions, such as hives or itching   | Type I  |
| Intradermal Test IgE | 15–20 minutes | Allergen injected under the skin surface       | Size of wheal and flare measured; smaller amounts injected | Immediate hypersensitivity reactions, like hives or anaphylaxis  | Type I  |
| Skin Patch Test      | 48–72 hours   | Allergens applied to patches on the skin       | Presence of localized skin reactions under the patches     | Delayed-type hypersensitivity reactions, like contact dermatitis | Type IV |

lowing complications: hypersensitivity, neurotoxicity, gastrointestinal issues, cardiovascular problems, hematological complications, skin toxicity, renal toxicity and toxicity, in the respiratory system [14].

## Hypersensitivity reactions to platinum agents

HSRs of platinum agents are mostly type I or type IV. For type I, the most expected symptoms will be diffuse erythroderma, wheezing, facial edema, gastrointestinal symptoms (nausea, vomiting, diarrhea), or anaphylaxis symptoms (dyspnea, hypotension). Contact dermatitis, maculopapular drug-induced rash, Stevens-Johnson syndrome, toxic epidermal necrolysis and interstitial nephritis may occur in IV HSRs associated with platinum agents [18].

## Hypersensitivity reactions to Taxanes

Hypersensitivity HSRs type II activation, supposedly triggered by their inactive ingredients: polyoxyethylated castor oil and Polysorbate 80 [19]. IgE type I reactions, in specific cases, usually occur after the first or second dose, commonly leading to back or pelvic pain. There were several case reports of acute liver injury associated with taxanes such as docetaxel and paclitaxel that occurred in patients experiencing acute hypersensitivity infusion reactions. Type III antigen–antibody complex formation causing urticarial vasculitis has been reported [22].

## Hypersensitivity reaction to asparaginase

There are 3 types of asparaginase: native L-asparaginase (L-ASP), derived from *Escherichia coli*, pegylated asparaginase (PEG-ASP), derived from *Escherichia coli* conjugated with polyethylene glycol; and Erwinia-ASP, derived from bacterial strains of *Erwinia chrysanthemi*. HRS is related to IgE antibody formation that may lead to anaphylaxis (Type I) as well as IgM or IgG antibody complex formation (Type III) [23, 24].

## Diagnostics of hypersensitivity reactions

Skin Prick Tests (SPTs) are routinely used in clinical practice; they are easy and fast to perform and are relatively safe and cheap [25]. SPT is a minimally invasive procedure that provokes histamine release in the skin via IgE-induced skin mast cell degranulation, leading to the generation of a wheal, which can then be measured. In a positive skin test, a mean wheal diameter  $\geq 3$  mm denotes sensitization to the tested

**Table 6. Comparison of dilution for prick test and intradermal tests [20]**

| Drug           | Prick Test Dilutions/Ratio                    | Intradermal Test Dilutions (mg/ml)                                     |
|----------------|---|--|
| Paclitaxel     | 1 part in 10                                  | 1 part in 1000 (0.001),<br>1 part in 100 (0.01),<br>1 part in 10 (0.1) |
| Docetaxel      | 1 part in 1                                   | 1 part in 100 (0.01),<br>1 part in 10 (0.1)                            |
| Carboplatin    | 1 part in 1                                   | 1 part in 100 (0.01),<br>1 part in 10 (0.1),<br>1 part in 1            |
| Cisplatin      | 1 part in 1                                   | 1 part in 100 (0.01),<br>1 part in 10 (0.1),<br>1 part in 1            |
| Oxaliplatin    | 1 part in 1                                   | 1 part in 100 (0.01),<br>1 part in 10 (0.1),<br>1 part in 1            |
| L-Asparaginase | A drop of reconstituted 5000 Kallikrein Units | 0.01 mL of reconstituted 5000 Kallikrein Units                         |

allergen but not necessarily clinical allergy [25, 27].

The Skin Patch Tests are the gold standard for detecting type IV HSRs, as it has high sensitivity and specificity between that ranges between 70–80% (Table 5) [28]. The recommendation varies in regards to the period of testing in that testing should be performed from 3 weeks to 6 months following the resolution of the eruption and the severity of cutaneous manifestations recommended.

Intradermal testing is utilized to evaluate IgE-mediated reactions, with immediate readings taken 15–30 minutes post-test. Conversely, for drug-induced T-cell-mediated immune responses, intradermal testing involves delayed readings conducted 48–96 hours after the test.

## Drug desensitization

Drug desensitization (DD) is a process where a problematic drug is given in progressively increasing doses until the total amount administered reaches the intended therapeutic dosage within a set duration. DD induces a temporary state of tolerance, during which the drug can be administered safely. DD has been recommended for immunoglobulin E (IgE)-mediated immediate hypersensitivity. However, its indications have recently been expanded to include non-IgE-mediated, non-immunological, or delayed T cell-mediated reactions [31].



Skin testing should usually be performed by an allergist to confirm hypersensitivity to a particular medication. There are different desensitization protocols (rapid, slow, multi-bag, or one-bag, with different target doses) suggested for each individual drug by an allergist. An appropriate desensitization protocol should be selected with consideration for concentration, dosage, dosing interval, and route of administration [32]. The treatment can be stopped immediately if any adverse reactions occur. The doses can then be readjusted, and treatment can continue using a different DD protocol. The procedure is always performed in an inpatient clinic where the patient can have immediate access to intubation and resuscitation if it is needed. In rare cases, a late-onset of DD may occur. It may manifest with serum sickness, anemia, nephritis and thrombocytopenia [33].

Patients are premedicated before DD with an agent to counter the specific hypersensitivity symptoms. H1 blockers, H2 blockers and glucocorticoids can be used as premedication. NSAIDs can help control the symptoms of possible cytokine release syndrome [34].

DD should be considered contraindicated in situations (Table 7) where the risks heavily outweigh the potential benefits. In immediate HSR, DD should be considered absolutely contraindicated in patients who have uncontrolled asthma or chronic obstructive pulmonary disease, those who are hemodynamically unstable, and those with poorly controlled cardiovascular disease.  $\beta$ -blocker or angiotensin-converting enzyme inhibitor (ACEI) treatment, previous serious anaphylactic reactions or chronic liver and kidney diseases that may put patients at high risk for a severe reaction when undergoing a procedure should be considered as relative contraindications. In delayed HSR, it is contraindicated in patients whose reaction suggests a history of severe cutaneous reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, drug induced hypersensitivity syndrome, drug rash with eosinophilia and acute generalized exanthematous pustulosis [35].

The result of DD is temporary and is only maintained through continually repeated exposure to the specific drug. DD has been performed successfully not only with chemotherapy drugs but also with antibiotics, antiretrovirals, antimycobacterials, vaccinations, insulin, hormonal therapy, monoclonal antibodies and other biologics [33].

## DISCUSSION

Allergists play a very important role in managing hypersensitivity reactions. The expertise lies inaccurately

**Table 7. High and low risk desensitization criteria [20]**

| Risk Level                               | Low Risk                                       | High Risk  |
|--|--|--|
| Grade of Hypersensitivity Reaction (HSR) | Grade I or Grade II                            | Grade III  |
| ST Status                                | Negative                                       | Positive   |
| Comorbidities                            | Absence of underlying health conditions        | Presence of: Respiratory pathologies, mastocytosis, cardiac pathologies: coronary disease, Arterial hypertension |
| Medications                              | Not treated with beta-blockers, ACE inhibitors | Treated with Beta-blockers, ACE inhibitors   |
| Pregnancy status                         | Not pregnant                                   | Pregnant   |

\*ST (skin test – skin prick test or/and intradermal test).

diagnosing allergic reactions, classifying the reaction into the correct type, and utilizing specialized tests like skin pricks intradermal tests, or even skin patch test. When the trigger is identified, allergists develop personalized treatment plans for patient which may include desensitization, premedication or alternative chemotherapy. Importantly, they educate and support patients, helping them understand their condition and manage it effectively over the long term. By offering expertise, support, and personalized care, allergists serve as invaluable allies in the journey of patients with chemotherapy agent hypersensitivity.

In medicine, the importance of identification of potential triggering factors and the understanding of cross-reactivity among substances stand as fundamental pillars for ensuring patient safety and effective treatment outcomes. When dealing with individuals who have a history of already confirmed hypersensitivity reactions, the meticulous assessment of medications and other substances becomes imperative to avoid triggering the cascade that will initiate an adverse reaction.

For example, the case of oral etoposide, which, on its own, does not usually induce hypersensitivity reactions. However, when considering Teniposide and intravenous etoposide, the solvents used such as cremophor and polysorbate 80 have been implicated as potential triggers for hypersensitivity reactions. This underlines the importance of not only examining the active ingredients of medications but also carefully considering the composition of their vehicles or carriers not to mention the importance of checking and rechecking the possibility of past reactions that should raise a red flag for an allergist [20].

Another example is the structural similarity between castor oil and Polysorbate 80 with components found in certain vaccines, including those that were developed to combat SARS-CoV-2. There was none to mild correlation between castor oil and Polysorbate 80 to SARS-CoV-2 vaccine components, suggesting the

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need for evaluation when considering vaccination in individuals with known sensitivities [21].

The Brigham and Women's Hospital's experience showed that 98.7% of the 232 DDs to platins were completed successfully, and the results showed that RDD was safe and effective. It was found a tendency that drug skin test positivity is a potential marker for identifying high-risk patients who will have BTRs during RDDs to platins. While SPTs with taxanes were mostly negative [33]. Furthermore, it was found that rapid DD for platinum-based chemotherapy drugs significantly increases peripheral blood IL-10 levels which is also known as human cytokine synthesis inhibitory factor (CSIF), an anti-inflammatory cytokine [34].

It is known that, in general, the incidence of HSRs to platinum or other agents increases as the number of administrations increases. Additionally, it has been reported that the combined use of liposomal doxorubicin and carboplatin is associated with a reduced HSR incidence rate when compared with combinations with paclitaxel and carboplatin alone, which suggests the possibility that liposomes have some impact on immune cells. However, the underlying mechanism for this remains unclear [35].

The future of desensitization is very important in allowing physicians to provide first-line therapies, contributing to a higher success rate in treatment. Looking to the future, advancements in desensitization techniques hold considerable promise in expanding treatment options for individuals with hypersensitivity reactions. By gradually exposing patients to allergens in controlled settings, desensitization therapies aim to build tolerance (temporary) and reduce the risk of adverse reactions. The continued refinement and widespread adoption of such techniques are revolutionizing the management of hypersensitivity disorders, allowing healthcare providers to deliver more personalized and effective care [36].

## CONCLUSIONS

Chemotherapy-induced hypersensitivity reactions are one of the main problems in the management of oncology diseases. Chemotherapy drugs are capable of inducing the various hypersensitivity reactions from mild cutaneous to severe respiratory and cardiovascular symptoms. Skin testing helps to diagnose drug hypersensitivity. Desensitization is beneficial for patients with confirmed hypersensitivity to chemotherapy drugs. Desensitization has a high success rate, allowing the attending physicians to keep their preferred first-line treatment. The role of an allergist is particularly important in the diagnosis and management of hypersensitivity to chemotherapy drugs.

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