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HYPERSENSITIVE REACTIONS TO CHEMOTHERAPY

HIPERSENZITIVNE REAKCIJE NA HEMIOTERAPIJU

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Abstract

Introduction. Despite advancements in therapeutic modalities, chemotherapy remains the cornerstone of treatment for a wide range of malignancies. However, all chemotherapeutic agents have the potential to induce hypersensitivity reactions. **Literature Review.** Platinum-based compounds and taxanes are the most frequently implicated in hypersensitivity reactions. The most commonly used classification systems for these reactions are the Brown classification and the Common Terminology Criteria for Adverse Events. Diagnostic approaches include *in vivo* provocation tests and in vitro assays. Optimal results from skin tests are achieved when performed between six weeks and six months after an allergic reaction. A positive skin test indicates a significant risk of anaphylaxis upon drug re-administration without precautionary measures. If no suitable alternative therapy is available, desensitization should be undertaken before reintroducing the drug. The process involves the controlled, stepwise administration of the drug, starting with a low dose and gradually increasing it under strictly monitored conditions. **Conclusion.** A thorough understanding the molecular mechanisms underlying hypersensitivity reactions, along with familiarity with their clinical presentation, classification, and diagnostic strategies, is essential for identifying suitable candidates for desensitization. Additionally, the involvement of a multidisciplinary team comprising allergists and oncologists is crucial in evaluating oncology patients and determining the most appropriate therapeutic approach for each individual case.

Key words: Antineoplastic Agents; Drug Therapy; Hypersensitivity; Desensitization, Immunologic; Skin Tests

Sažetak

Uvod. Uprkos novim terapijskim modalitetima, hemioterapija i dalje predstavlja okosnicu lečenja širokog spektra zloćudnih bolesti, a svi hemioterapijski agensi mogu izazvati reakcije preosetljivosti. **Pregled literature.** Najveći broj hipersenzitivnih reakcija uzrokuju jedinjenja platine i taksani. Najčešće korišćene klasifikacije hipersenzitivnih reakcija su Braunova klasifikacija i Zajednički terminološki kriterijumi za neželjena dejstva. Dijagnostički testovi se dele na *in vivo* provokacione testove i in vitro testove. Najbolje rezultate dobijamo ukoliko kožne testove sprovodimo u periodu od šest nedelja do najkasnije šest meseci od alergijske reakcije. Pozitivni rezultati kožnih testova pokazuju da je pacijent pod značajnim rizikom od anafilaksije ako se lek ponovo primeni bez mera opreza. Pre ponovne primene leka potrebno je sprovesti desenzibilizaciju ukoliko ne postoji ekvivalentna supstituciona terapija. Desenzibilizacija uključuje ponovnu primenu leka u visokokontrolisanim uslovima, koristeći postupne korake u kojima se najpre primenjuje niska doza leka, a kroz svaki sledeći korak doza se postepeno povećava. **Zaključak**. Razumevanje molekularnih mehanizama hipersenzitivnih reakcija, poznavanje njihove kliničke slike i klasifikacije, kao i poznavanje dijagnostičkih testova ključni su za pravilan odabir bolesnika za desenzibilizaciju. Važno je naglasiti važnost multidisciplinarnog tima alergologa i onkologa u evaluaciji onkoloških bolesnika i donošenju odluka za primenu najboljeg terapijskog modaliteta za svakog pojedinog bolesnika.

Ključne reči: hemioterapijski agensi; hemioterapija; hipersenzitivna reakcija; imunološka desenzitizacija; kožni testovi

Introduction

For nearly nine decades, chemotherapy has played a pivotal role in the treatment of malignant diseases. Despite advancements in therapeutic modalities, it remains the cornerstone of cancer treatment [1, 2]. However, all chemotherapeutic agents have the potential to induce hypersensitivity reactions (HCR), which are the third leading cause of fatal drug-induced anaphylaxis in the United States [2]. Therefore, whenever feasible, chemotherapy should be limited in favor of targeted therapies [3]. Platinum-based compounds and taxanes account for the majority of HCR cases, which may be mediated by IgE-dependent or non-IgE mechanisms and present with varying clinical manifestations. Prompt recognition and management of life-threatening hypersensitivity reactions are crucial. Identifying high-risk patients allows for proper risk assessment and informed decision-making regarding further treatment [4]. Desensitization is a safe and highly effective strategy, with breakthrough reactions occurring infrequently and typically presenting as mild [5].

Literature review

Platinum derivatives

Among chemotherapeutic agents, platinum derivatives are the most common triggers of HCR [2].

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Abbreviations

HCR – hypersensitive reactions
IgE – immunoglobulin E
BRCA 1/2 – breast cancer gene
IL-6 – interleukin six
TNF-α – tumor necrosis factor alpha
SCAR – Severe Cutaneous Adverse Reactions
SJS/TEN – Stevens-Johnson syndrome/toxic epidermal necrolysis
CT – computed tomography
IL-1ß – interleukin one beta
CTCAE – Common Terminology Criteria for Adverse Events
ACE – angiotensin converting enzyme

The primary platinum-based drugs include cisplatin, oxaliplatin, and carboplatin, while nedaplatin, heptaplatin, and lobaplatin are available only in Asia [1] **(Table 1)**.

Published data indicate that over 20% of patients receiving platinum-based chemotherapy experienced allergic reactions [6]. The most significant risk factor for HCR to platinum agents is prior exposure, with incidence rates increasing from 1% after the first six cycles to 27% beyond the seventh cycle of carboplatin. The peak occurrence is observed around the eighth or ninth cycle [8], with similar patterns reported for cisplatin and oxaliplatin [7]. Additionally, increased HCR rates have been noted in women with BRCA 1/2 mutations [1, 2, 9]. In pediatric patients receiving carboplatin for brain tumors, the incidence of HCR has been reported at 42% [10].

Cross-reactivity between carboplatin and oxaliplatin is estimated at 37-45%, whereas patients who experience HCR to either drug have a significantly lower risk when switched to cisplatin due to it minimal cross-reactivity [10]. Nedaplatin has been explored as an alternative for patients with carboplatin-induced HCR. A recent study confirmed its favorable safety profile, with only one reported case of HCR [1].

The majority of platinum-induced HCR are IgE-mediated type I hypersensitivity reactions, initially described in refinery workers exposed to platinum salts. This was later confirmed by the detection of carboplatin-specific IgE antibodies [11]. Immediate

Table 1. Characteristics of immediate hypersensitive reactions on platinum derivatives

Chemotherapeutic agent	Malignancies in which it is used	Time to HCR onset	Characteristics of HCR
Carboplatin	• Ovarian cancer • Lung cancer • Squamous cell carcinoma of head and neck	Maximum rate of HCR occurs when applying the 8th or 9th cycle • 1% between 1-6th cycle • 27% when applying for the 7th cycle or subsequent ones	Redness, itching, urticaria Approximately 50% of HCRs are moderately severe with diffuse erythroderma, wheezing, facial swelling, nausea/vomiting, diarrhea, dyspnea, hypotension, or anaphylaxis
Cisplatin	• Gynecological malignancies • Lung cancer • Squamous cell carcinoma of head and neck	Increases with the number of cycles and simultaneous irradiation; higher rate after the 6th cycle	Urticaria, itching, respiratory distress, hypotension
Oxaliplatin	Gastrointestinal malignancies, especially colon cancer in combination with leucovorin and fluorouracil (FOLFOX)	Increases with the number of cycles; up to 20% after the 6th cycle	Flushing, pruritis, urticaria, palmar erythema, angioedema, hypertension, hypotension, dyspnea, chest tightness, cough, throat tightness, nausea, diarrhea. Less often - temperature, chills, shivering, stiffness, back pain. Neurological (tingling, dizziness). Rarely, thrombocytopenia, hemolytic anemia, and bleeding.
Albumin bind paclitaxel Cremofor bind Paclitaxel Docetaxel	• Breast cancer • Ovarian cancer • Non-small cell lung cancer • Squamous cell cancer of head and neck • Kaposi sarcoma (paclitaxel) • prostate cancer (docetaxel) • Stomach adenocarcinoma (docetaxel) • Adenocarcinoma of pancreas (paclitaxel)	At first exposure during the 1st or 2nd cycle	Flushing, chest pain, back pain, abdominal pain, respiratory symptoms (dyspnea, chest tightness, wheezing, throat tightness), gastrointestinal symptoms (nausea, vomiting, diarrhea), hypertension, hypotension, fluid retention.
Cabizataxel	Second line metastatic, hormone resistant, prostate cancer		

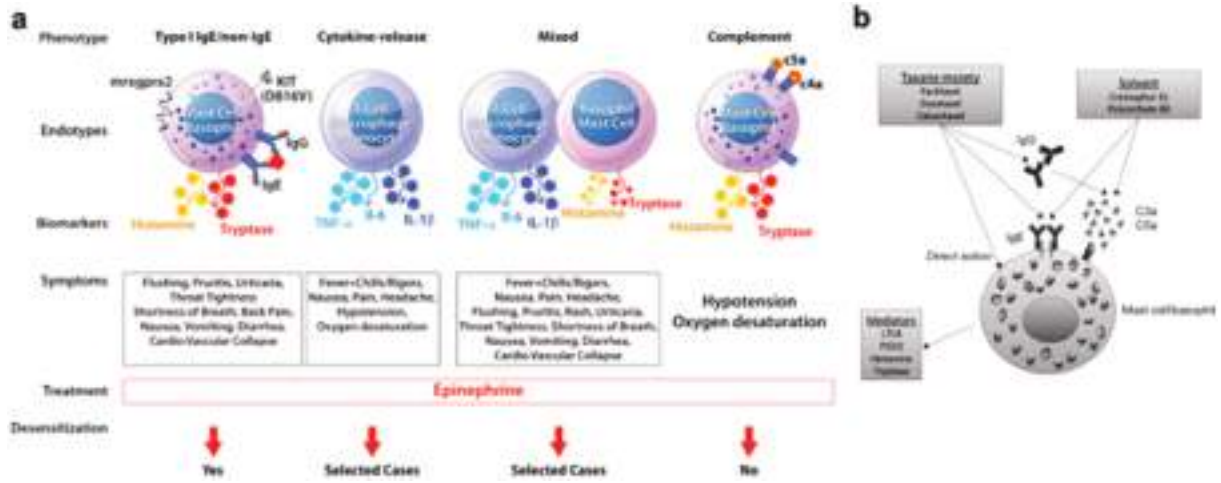

Figure 1. Mechanisms of immediate hypersensitive reactions on platinum and taxanes. Available at: https://doi.org/10.1007/s12016-021-0887

reactions commonly present as pruritus of the palms and soles, erythema and urticaria. However, platinum agents have also been associated with several cases of type II hypersensitivity reactions, such as immune-mediated hemolytic anemia and thrombocytopenia (with oxaliplatin), sometimes complicated by bleeding, and type III hypersensitivity reactions, including delayed urticaria as part of vasculitis.

Skin testing and desensitization play no role in type II and type III hypersensitivity reactions, but the drug should be permanently discontinued [10].

A new classification of HCR integrates phenotypes, endotypes and biomarkers. Phenotypes of platinum-induced HCR **(Figure 1)** include immediate and delayed reactions, categorized into type I hypersensitivity reactions, cytokine release reactions, and mixed reactions, with the greatest heterogeneity observed with oxaliplatin [7]. Endotypes define the underlying immunological mechanisms, while biomarkers facilitate their identification [6]. Oxaliplatin-induced HCR are particularly heterogeneous, often presenting as cytokine release reactions characterized by fever, chills, rigors, headache, chest pain, or back pain, accompanied by elevated IL-6 and TNF-α levels [12].

Taxanes

Taxanes are complex alkaloid esters used in the treatment of various malignancies including breast, prostate, head and neck, lung, and gynecological cancers. The main taxanes include paclitaxel, docetaxel, nab-paclitaxel, and cabazitaxel. Paclitaxel was originally derived from the Pacific yew tree, while docetaxel is produced via a semisynthetic process [13]. Although structurally similar, taxanes differ in their solvents>: paclitaxel is formulated with Cremofor EL, whereas docetaxel and cabazitaxel use polysorbate 80 [2]. Cremofor EL has been shown to induce direct complement activation, leading to the release of anaphylatoxin and subsequent mast cell and basophil activation. In patients with prior anaphylactic reactions to docetaxel and paclitaxel, the use of nanoparticles bound to albumin (nab-paclitaxel), which lacks Cremofor EL, has been associated with a lower incidence of HCR [2]. However, severe immediate HCR have still been reported with nab-paclitaxel [7].

Taxanes are highly allergenic, with early studies reporting immediate HCR rates as high as 50% for paclitaxel and docetaxel, prompting the routine use of antihistamines and corticosteroids for premedication [13]. Most HCR occur within minutes, typically during the first or second exposure to the drug [7]. Cross-reactivity between paclitaxel and docetaxel has been reported in two studies, and an association between taxanes and tryptase allergens has been demonstrated [14]. One example of IgE-mediated HCR involves individuals previously exposed to yew pollen, who may develop hypersensitivity to taxanes [13]. Additionally, paclitaxel has been isolated from hazelnuts, and cases of cross-reactivity between paclitaxel and hazelnut consumption have been documented [15, 16].

Immediate HCR to paclitaxel and docetaxel occur in approximately 10% of patients, with severe reactions reported in 1% of cases despite premedication [7, 8, 17]. Symptoms typically manifest 15 minutes after infusion onset and include dyspnea (with or without bronchospasm), urticaria, hypotension (or hypertension), delayed erythematous rash (which may begin hours or weeks after drug application), and severe pain in the back, pelvis, chest, and abdomen [7, 8, 18]. Unlike platinum agents, 90% of taxane-induced HCR occur within the first two treatment cycles [1]. This pattern suggests a mechanism involving direct process

of mast cell degranulation. A case report described a fatal anaphylactic reaction to paclitaxel, where the patient experienced lip swelling and urticaria ten days after chemotherapy administration [19].

In 10-15% of cases, HCR to taxanes present as delayed skin reactions, emerging – several days up to 10 days post-administration of docetaxel. These reactions range from mild maculopapular exanthema, urticaria, and angioedema to severe cutaneous adverse reactions (SCAR) and may also involve other organs such as the lungs, liver, and kidneys [6]. Most of the mild reactions resolve within a few days with symptomatic treatment [10]. However, severe delayed reactions to paclitaxel include interstitial pneumonitis, which is associated with for a high risk of mechanical ventilation and mortality [20]. Severe reactions such as Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), acute interstitial pneumonitis, and subacute cutaneous lupus erythematosus have been documented with paclitaxel, docetaxel, and nab-paclitaxel [8, 13].

Interstitial pneumonitis may develop days to weeks after docetaxel and paclitaxel administration, occurring less frequently with nab-paclitaxel and docetaxel. Clinical manifestations include exertional dyspnea, dry cough, fatigue, and low-grade fever. High-resolution CT (HRCT) typically reveals ground-glass opacities, which may be diffuse or present as centrilobular nodules, corresponding to non-fibrotic hypersensitivity pneumonitis. In contrast, fibrotic hypersensitivity pneumonitis is characterized by traction bronchiectasis, bronchioloectasis, honeycombing, and bronchiolitis, with HRCT findings displaying the "headcheese" or "triple density" sign [21]. Management is primarily supportive, with taxane discontinuation at the first step. The initiation of glucocorticoid therapy depends on the severity and progression of lung involvement [22].

Another notable adverse effect is capillary leak syndrome, observed with docetaxel. It is characterized by peripheral edema, dyspnea, non-cardiogenic pulmonary edema, and pleural effusions, with weight gain often being the earliest sign. Prompt diuretic therapy at symptom onset may help prevent severe fluid retention complications [22].

Immediate HCR typically occur within 1-6 hours post-administration, and this phenotype is most often associated with either IgE-mediated endotype or the endotype of direct complement activation. Delayed type IV hypersensitivity reactions, which appear days to weeks after drug exposure, most commonly manifest as maculopapular exanthema or severe SCAR [6]. Solvent taxanes such as Cremofor EL (paclitaxel) and polysorbate 80 (docetaxel) can activate mast cells either via an IgE-mediated mechanism or through direct complement activation, leading to C3a and C5a anaphylatoxin release **(Figure 2)**. Additionally, histamine release has been observed during the direct action of paclitaxel on basophils [13]. Biomarkers include: tryptase, histamine, leukotrienes and prostaglandins in type I reactions, and IL-6, TNF-α and IL-1ß

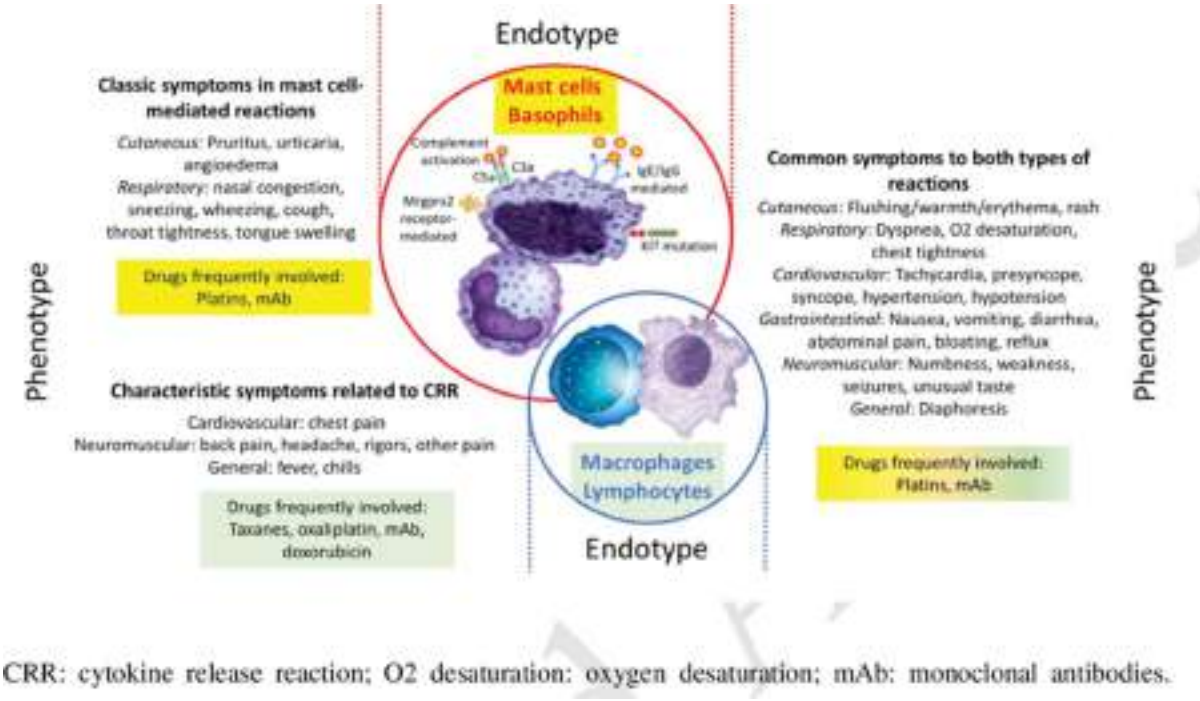

Figure 2. Phenotypes and endotypes of hypersensitive reactions to chemotherapy and monoclonal antibodies. Available at: https://pubmed.ncbi.nlm.nih.gov/34045179/

in cytokine release or mixed reactions [1, 7]. Desensitization is indicated for type I reactions and selected cases of cytokine release or mixed reactions. However, it is not effective for reactions caused by direct mast cell or basophil activation [7].

Classification of HCR

Classifying hypersensitivity reaction is essential for assessing severity and guiding therapeutic decisions. The most widely used classifications are the Brown classification and the Common Terminology Criteria for Adverse Events (CTCAE) [7].

Diagnosis

Classifying hypersensitivity reaction diagnosis is based on clinical history, physical examination, symptomatology, and diagnostic tests. These tests are categorized into in vivo provocation tests and in vitro tests. In vivo provocation tests include skin (prick and intradermal) and dose provocation tests. Skin tests are sensitive, widely used, cost-effective, and rapid methods for detecting IgE-mediated allergic reactions. Their main advantages over in vitro tests are their immediacy (results within 15 to 20 minutes), and patient involvement, enhancing understanding of allergic responses [23]. The most extensively studied agents for skin testing are platinum derivatives and taxanes [1]. Other antineoplastic agents can also be tested, provided that they do not induce skin necrosis upon extravasation. Irritant drugs must be diluted appropriately to prevent non-allergic skin irritation. Testing begins with a prick test, followed by an intradermal test if the prick test is negative [10]. Intradermal testing involves injecting a small drug dose into the dermis, increasing sensitivity due to enhanced exposure of cutaneous mast cells [1]. However, several systemic reactions have been reported during intradermal testing [23]. These reactions result from histamine release, leading to smooth muscle contraction and increased vascular permeability. At the same time, inflammatory mediators activate neuron reflex mechanisms, with secondary vasodilatation and erythema [1].

Patients with a history of severe HCR to platinum derivatives should undergo skin testing before re-exposure. If positive, desensitization is necessary [10]. Carboplatin and oxaliplatin skin tests are particularly valuable for predicting HCR risk during desensitization, as positive test results correlate with an increased likelihood of recurrent reactions [2]. Intradermal testing is necessary with carboplatin as 86.4% of positive skin tests are confirmed through this method [7, 11]. The concentrations used for testing affect the predictive value of skin tests. Lower concentrations (1-5 mg/mL) yield 41-75% positivity, while 10 mg/ml increased detection rates to 81-88% [7].

Optimal testing occurs 6 weeks to 6 months after HCR; delays beyond six months increase false-negative results. The time period between the performance of the skin test and prior exposure to carboplatin or HCR is important for test result interpretation. Testing is recommended at least 4-6 weeks after the initial HCR, although some studies suggest a 2–week window [11, 22]. However, false negative results may occur. In one study, 5 of 37 (13.5%) patients tested negative within 10 days of immediate HCR but later converted to positive on repeat testing [24].

Positive skin test results indicate high anaphylaxis risk if the drug is re-administered without precautions. Desensitization is required before re-administration of the drug if no alternative therapy exists [10]. Negative skin test results allow for drug re-administered under lower-concentration protocols, gradual dose increase, and additional premedication [10].

If previous standard tests are negative or unavailable, and after a careful risk–benefit assessment, a dose challenge test may be performed – the gold standard for diagnosing HCR [1]. Dose challenge test with platinum derivatives involves administering 1/10 of the full dose at the normal infusion rate without premedication, observing for 30 minutes for any reaction, and if no symptoms appear, administering the remaining 9/10 of the dose. If no symptoms appear, the absence of allergy is concluded and future drug use is allowed [10]. Contraindications for dose challenge test include uncontrolled asthma, pregnancy, beta-blocker use, cardiac disease history, vasculitis, bullous exanthemas, acute generalized exanthematous pustulosis, and severe anaphylaxis history [1].

In vitro tests include determination of specific IgE (sIgE), total IgE (tIgE), basophil activation test (BAT), and tryptase measurement [1]. Mast cells and basophils contain various chemical mediators that are released into the circulation during anaphylaxis. Serum tryptase concentration peaks 3 hours post reaction. Testing within 1-3 hours of symptom onset is recommended as earlier samples (< 30 minutes) may yield false negatives [10]. The lymphocyte transformation test in vitro assesses T-cell proliferation in response to an antineoplastic drug but is technically demanding clinically. The specific IgE test for oxaliplatin was validated in 2015 through a prospective study. For platinum derivatives, specific IgE testing is important for diagnosis (recommendation level B) [2]. Skin testing and measuring the level of chemical mediators are crucial for evaluating HCT during desensitization [10].

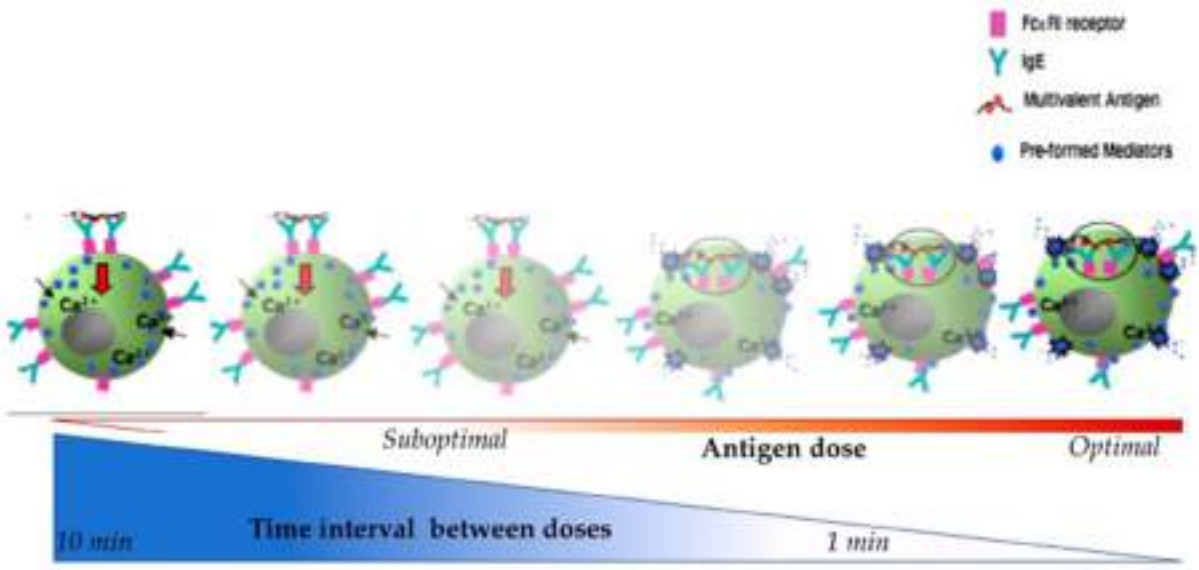

Figure 3. Schematic diagram showing mast cell β-hexosaminidase in relation to time interval between antigen administration and antigen dose during desensitization. Available at: https://pmc.ncbi.nlm.nih.gov/articles/PMC5486137/

Desensitization

The origins of desensitization trace back to the 1980s when the first intravenous and oral penicillin desensitization protocols were established [6]. Desensitization involves the controlled re-administration of a drug in gradually increasing doses, starting with a low initial. The process must be repeated each time the drug administered [10]. The time intervals and dosage increments during desensitization are crucial. If suboptimal doses are administered every minute, mediator inhibition is reduced, whereas ten-minute intervals maximize inhibition **(Figure 3).** Additionally, suboptimal doses cause less mediator release than optimal doses. Shorter intervals or excessively high suboptimal dose can increase β-hexosaminidase release, leading to breakthrough reactions (when the drug is applied too quickly) [6]. Desensitization is contraindicated in cases of exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and immune thrombocytopenia caused by chemotherapy [2]. Patients are stratified into high- and low-risk groups based on specific risk factors. The high-risk group includes pregnant women, patients with positive skin tests or Grade III HCR, and those on beta-blockers or ACE inhibitors. It also includes individuals with comorbidities such as cystic fibrosis, mastocytosis, coronary disease, or hypertension [2].

Desensitization must be conducted by an allergist or in an intensive care unit to allow for immediate anaphylaxis management. Rapid desensitization protocols are not recommended for patients with IgE-mediated anaphylactic reactions, particularly those related to platinum derivatives. During desensitization, mild symptoms commonly occur, especially in the later stages of drug administration [10]. Mast cell unreactivity has been attributed to impaired FcεR1 receptor internalization due to progressive cross-linking at low antigen concentration, indicating that the receptors are exhausted before the next dose. Unlike in activated cells, where antigen/IgE/FcεR1 complexes are internalized, these complexes remain on the surface during desensitization [6].

According to Leticia de las Vecillas Sanchez and colleagues, rapid desensitization inhibits mast cell activation in all fields by impairing antigen/IgE/FcεR1 complex internalization, preventing calcium flux, and releasing lipid mediators, and cytokine production [6].

Conclusion

A comprehensive understanding of the molecular mechanisms of hypersensitive reactions, their clinical presentation, classification, and diagnostic methods is essential for selecting appropriate candidates for desensitization. Risk assessment and prompt intervention in case of severe anaphylactic reactions are crucial. A multidisciplinary team of allergists and oncologists plays a pivotal role in evaluating oncology patients and determining the most suitable therapeutic approach for each individual case.

References

1. Galateanu B, Pușcașu AI, Tircol SA, Tanase BC, Hudita A, Negrei C, et al. Allergy in cancer care: antineoplastic therapy-induced hypersensitivity reactions. Int J Mol Sci. 2023;24(4):3886.

2. Pagani M, Bavbek S, Alvarez-Cuesta E, Berna Dursun A, Bonadonna P, Castells M, et al. Hypersensitivity reactions to chemotherapy: an EAACI Position Paper. Allergy. 2022;77(2):388-403.

3. Brdar-Zelen T, Jovisevic M, Prica A. Use of cyclin-dependent kinase 4 and 6 inhibitors in treating metastatic breast cancer - a year-long experience in Subotica General Hospital in patient follow-up. Med Pregl. 2024;77(3-4):94-9.

4. Tham EH, Cheng YK, Tay MH, Alcasabas AP, Shek LP. Evaluation and management of hypersensitivity reactions to chemotherapy agents. Postgrad Med J. 2015;91(1073):145-50.

5. Vega A, Jimenez-Rodriguez TW, Barranco R, Bartra J, Diéguez MC, Doña I, et al. Hypersensitivity reactions to cancer chemotherapy: practical recommendations of ARADyAL for diagnosis and desensitization. J Investig Allergol Clin Immunol. 2021;31(5):364-84.

6. de Las Vecillas Sánchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug hypersensitivity and desensitizations: mechanisms and new approaches. Int J Mol Sci. 2017;18(6):1316.

7. Tsao LR, Young FD, Otani IM, Castells MC. Hypersensitivity reactions to platinum agents and taxanes. Clin Rev Allergy Immunol. 2022;62(3):432-48.

8. Broyles AD, Banerji A, Barmettler S, Biggs CM, Blumenthal K, Brennan PJ, et al. Practical guidance for the evaluation and management of drug hypersensitivity: specific drugs. J Allergy Clin Immunol Pract. 2020;8(9S):S16-116.

9. Moon DH, Lee JM, Noonan AM, Annunziata CM, Minasian L, Houston N, et al. Deleterious BRCA1/2 mutation is an independent risk factor for carboplatin hypersensitivity reactions. Br J Cancer. 2013;109(4):1072-8.

10. Castells MC, Matulonis UA, Horton TM. Infusion reactions to systemic chemotherapy [Internet]. 2023 [cited 2025 Jan 16]. Available from: https://www.uptodate.com/contents/infusion-reactions-to-systemic-chemotherapy

11. Lax T, Long A, Banerji A. Skin testing in the evaluation and management of carboplatin-related hypersensitivity reactions. J Allergy Clin Immunol Pract. 2015;3(6):856-62.

12. 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(5):1668-80.e2.

13. Picard M, Castells MC. Re-visiting hypersensitivity reactions to taxanes: a comprehensive review. Clin Rev Allergy Immunol. 2015;49(2):177-91.

14. 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.

15. Hoffman A, Shahidi F. Paclitaxel and other taxanes in hazelnut. J Funct Foods. 2009;1(1):33-7.

16. Bukacel DG, Bander R, Ibrahim RB. Cross-reactivity between paclitaxel and hazelnut: a case report. J Oncol Pharm Pract. 2007;13(1):53-5.

17. Bonamichi-Santos R, Castells M. Diagnoses and management of drug hypersensitivity and anaphylaxis in cancer and chronic inflammatory diseases: reactions to taxanes and monoclonal antibodies. Clin Rev Allergy Immunol. 2018;54(3):375-85.

18. Pagani M, Bavbek S, Dursun AB, Bonadonna P, Caralli M, Cernadas J, et al. Role of skin tests in the diagnosis of immediate hypersensitivity reactions to taxanes: results of a multicenter study. J Allergy Clin Immunol Pract. 2019;7(3):990-7.

19. A fatal anaphylactic reaction to paclitaxel is described, which was preceded by a possible delayed reaction to the initial infusion. Allergy Asthma Proc. 2011;32(1):79.

20. Syrigou E, Dannos I, Kotteas E, Makrilia N, Tourkantonis I, Dilana K, et al. Hypersensitivity reactions to docetaxel: retrospective evaluation and development of a desensitization protocol. Int Arch Allergy Immunol. 2011;156(3):320-4.

21. Churg A. Hypersensitivity pneumonitis: new concepts and classifications. Mod Pathol. 2022;35(Suppl 1):15-27.

22. King TE. Taxane-induced pulmonary toxicity [Internet]. 2023 [updated 2024 Apr 30; cited 2025 Jan 16]. Available from: https://www.uptodate.com/contents/taxane-induced-pulmonary-toxicity

23. Kowal K, DuBuske L. Overview of skin testing for IgE-mediated allergic disease [Internet]. 2022 [cited 2025 Jan 16]. Available from: https://www.uptodate.com/contents/overview-of-skin-testing-for-ige-mediated-allergic-disease

24. Ang WX, Church AM, Kulis M, Choi HW, Burks AW, Abraham SN. Mast cell desensitization inhibits calcium flux and aberrantly remodels actin. J Clin Invest. 2016;126(11):4103-18.

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