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Annals of Immunology & Immunotherapy
ISSN: 2691-5782

The Importance of Drug Desensitization in Cancer

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Review Article
Volume 3 Issue 2
Received Date: August 03, 2021
Published Date: August 19, 2021
DOI: 10.23880/aii-16000145

Abstract

Drug hypersensitivity reactions (HSRs) to antineoplastic agents have increased in the 21st century with the emergence of new therapeutic agents. Rapid drug desensitization (RDD) to chemotherapeutic agents and monoclonal antibodies (mAbs) has emerged as a safe and effective strategy for those patients who develop HSRs to their necessary medication, given their limited therapeutic options.

Drug desensitization (DS) induces a temporary tolerance to the drug, allowing the patient with an HSR to safely receive an uninterrupted course of medication. The knowledge of the recently described new phenotypes, within HSRs, with their corresponding endotypes and biomarkers, provides a better diagnostic approach and more accurate risk stratification for a more secure and effective desensitization protocol. In addition, premedication can be tailored according to the phenotype, endotype and biomarkers of the reaction.

Any desensitization should always be carried out with maximum safety in mind and adapted to the care organization of each allergy department. Desensitization is a temporary process, once the medication is discontinued the patient's hypersensitivity to the medication returns.

Objective: The aim of this review is to briefly summarize updated information on the mechanisms of desensitization, indications, contraindications, risk stratification and treatment of reactions during desensitization to chemotherapeutic drugs and mAbs. Also to emphasize the importance of maintaining the first-line of treatment in cancer patients, thus improving the patient's life expectancy and quality of life.

Keywords: Desensitization; Drug Hypersensitivity; Chemotherapy; Monoclonal Antibodies in Cancer; Platins; Taxanes

Introduction

The development of new advances in cancer at a molecular and genomic level have resulted in the creation of new chemotherapeutic agents, monoclonal antibodies (mAbs), and other targeted treatments that can potentially induce hypersensitivity reactions (HSR). Allergic reactions to these drugs are unexpected, can be severe and compromise first-line therapies that are critical for patient's life expectancy and quality of life [1].

Rapid drug desensitization (RDD) to chemotherapeutic agents and mAbs has emerged as a powerful, safe and effective re-administration strategy for those patients who develop HSRs to their needed medication, given their limited therapeutic options [2]. Hence the importance of understanding the mechanisms and main aspects of drug desensitization (DS).

Classification of Drug Hypersensitivity Reactions

Traditionally, drug HSRs were divided broadly into 4 categories according to the Gell and Coombs classification [3], but they did not encompass the current spectrum of symptoms occurring in patients treated with chemotherapeutic agents and biological drugs [4,5]. Recently, a new classification of drug HSRs has been described to provide a new operational categorization based on the clinical phenotypes, the corresponding endotypes and the associated biomarkers [6]. This new classification includes immediate reactions with IgE or non-IgE-involvement, cytokine release reactions (CRRs) and mixed patterns. As for the delayed reactions, they remain as they were described in the Gell and Coombs classification (types II, III and IV HSRs) [1,7].

The phenotype of a reaction refers to the clinical features of the episode that can appear by multiple mechanisms [7,8]. Phenotype of type I (IgE or non-IgE-mediated) reactions includes flushing, pruritus, urticaria, angioedema, glottic closure, respiratory distress, bronchospasm, nausea, vomiting, diarrhea, hypotension or syncope. The phenotype of CRRs comprises fever, chills, nausea, headache, muscle or joint pain, hypotension or desaturation [9]. Some patients present mixed reactions of both, type I and CRRs features. The type of drug exposure, the time of onset and the reaction severity help to characterize the phenotype of a reaction.

The immunological mechanisms underlying the reaction refer to the endotype [6]. Several different endotypes are now recognized for both immediate and delayed forms of drug hypersensitivity [8]. Mast cells activation through multiple routes (IgE mediated mechanisms, IgG antigen interactions, activation of MRGPRX2 receptors and complement cascade activation) corresponds to the endotype in immediate type I reactions [4]. The endotype in the immediate reactions by CRRs, refers to the release of pro-inflammatory cytokines. In such reactions, the cytokine release may come from multiple cellular types, including T cells, monocytes, and macrophages [8].

Biomarkers are the characteristics that allow measuring the different physiologic, pathogenic or pharmacological responses to treatments. Skin testing and serum specific IgE are informative with immediate reactions believed to be mast cell mediated. The basophil activation test (BAT) is considered a true reflection of sensitized mast cells, but its sensitivity and specificity vary widely. Serum tryptase is the most widely used and available marker of mast cell degranulation, however it does not shed light on the mechanism of mast cell triggering. Elevated levels of cytokines such as tumor necrosis factor alpha (TNFa), interleukin-6 (IL-6), or interleukin-1b (IL-1b) are detected in patients with CRRs. As many different cell types can secrete these cytokines, a cytokine release phenotype may be entirely unrelated to mast cells or be due to a mixed endotype [8,9].

Recognizing phenotypes, endotypes and biomarkers is crucial to provide a more personalized approach to RDD [10].

Mechanisms of Drug Desensitization

The cellular and molecular pathways through which desensitization induce a temporary tolerance to a drug is not well known as they have only been studied in IgE-mediated drug HSRs. In vivo and in vitro models have evidenced that the incremental escalation of sub-optimal doses of the offending drug at a sufficient time interval inhibits the activation of mast cells and basophils, limiting signal transduction and the release of pro-inflammatory mediators [11]. Thus, the desensitization procedure is associated with the inhibition of:

- Early-phase mast cell activation, so b-hexosaminidase and pre-formed TNFa release in desensitized mast cell show a significant reduction.
- The mobilization of intracellular calcium, this inhibition being antigen-dependent.
- The metabolization of arachidonic acid, so there is no generation of lipid mediators (prostaglandins and leukotrienes).
- The secretion of de novo synthesized TNFa and IL-6 in the late phase response.

Four possible mechanisms have been proposed to explain how mast cell inhibition occurs during desensitization [7]:

- Absence of internalization of the Ag/IgE/FceRI (antigen/IgE/high affinity receptor for the IgE) complexes.
- Decreased intracellular calcium influx into mast cell.
- Alteration of the balance between activating and inhibitory pathways: ITAM/ITIM (immune-receptor tyrosine-based activation/inhibition motif).
- Participation of aberrant actin cytoskeleton reorganization in calcium mobilization, which would prevent mediator release during desensitization [12].

Drug Desensitization: Definitions, Indications and Contraindications

DS is defined as the process by which a temporary tolerance state to a drug responsible for a hypersensitivity reaction is induced, through the administration of progressively increasing doses of the responsible drug, until the required therapeutic dose is reached. Desensitization protocols have been developed to achieve full therapeutic doses of drug allergens without eliciting life-threatening symptoms. It is a personalized risk procedure, specific for each drug, which maintains the effectiveness of the drug [13,14].

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DS should be considered when the medication concern is irreplaceable, as its non-administration implies an immediate, or possible, life risk to the patient; when the drug has a primary indication, due to the lack of, or less effective, therapeutic alternative; or, when there is no other drug from the same therapeutic group without cross-reactivity [13].

Depending on the type of reaction, desensitization is indicated in immediate hypersensitivity reactions produced by (i) the release of mast cell and basophil mediators, whether they are due to an IgE-mediated mechanism or are produced by mechanisms not mediated by IgE, (ii) the release of cytokines and (iii) in those of mixed type. It is also indicated in late type IV reactions associated with a maculopapular rash [15]. Desensitization is contraindicated in severe cutaneous adverse reaction (SCAR) as Dress Syndrome, Steven-Johnson Syndrome, toxic epidermal necrolysis (TEN), acute generalized exanthematous pustulosis (AGEP), systemic vasculitis or severe mucosal ulcers, as well as in drug-induced autoimmune disorders, in cases of drug-induced systemic symptoms (fever, arthritis, generalized lymphadenopathy) and in reactions including severe involvement of a vital organ or system (type II and III reactions) such as hepatitis, nephritis, pneumonitis, cytopenias or severe eosinophilia [13,14].

Risk Stratification and Initial Premises to Perform Drug Desensitization

Desensitization poses a risk of developing a HSR and should therefore be performed in a safe environment under the supervision of a trained physician who is familiar with the procedure and treatment of anaphylaxis [1]. Patient constants should be continuously monitored and the patient must be properly informed about the procedure and have signed the informed consent.

Although most RDD are successful and most of the reactions that occur during desensitization are less severe than the reactions that prompted the study, more serious reactions cannot be ruled out during the process. Desensitization should therefore be considered a high-risk procedure, which should be individualized, assessing the risk / benefit of the treatment in each patient.

In order to evaluate the risk/benefit of performing desensitization and the most appropriate type of protocol for each patient an indivdual adequate risk stratification assesment should be developed taking into account the following issues: the initial reaction (according to Brown's classification) [16]; phenotype and endotype related factors and both in vivo and in vitro biomarkers; specific patient characteristics (patient's age and comorbidities) as well as his/her usual medication; social factors of the patient (travel distance to the desensitization center or his/her anxiety level); and, consideration of the culprit drug and whether more than one drug was involved in the reaction. All these factors will made a safer anf more effective protocol [17].

Main Desensitization Protocols with Chemotherapeutic Agents and Monoclonal Antibodies

The most commonly used intravenous protocol is based on 3 bags and 12 steps, with three different solutions at 100-fold, 10-fold, and 1-fold dilution of the final target concentration [18]. The desensitization process consists in the administration of sequential x2 to x2.5 doses of the drug antigens at fixed time intervals (usually every 15 minutes); doubling the doses is the true nature of this process. This protocol is flexible and can be tailored following the patient's initial reaction. In high-risk situations or patients with severe HSRs, 16-step (4 bags) or 20 step protocols can be performed, while shorter protocols with only 8 steps (2 bags) have been proposed in patients with a mild-to-moderate risk [13]. Protocols are also available for oral, subcutaneous, or intraperitoneal routes.

Premedication is recommended before the administration of the drug in order to prevent or decrease the severity of reactions during desensitization. Its fundamental goal is to block the effect of mast cell mediators: antihistamines block histamine receptors; acetylsalicylic acid acts against prostaglandin D2 and montelukast or zileuton against leukotrienes. The greatest benefit of pretreatment with acetylsalicylic acid and montelukast was seen in patients with skin and respiratory symptoms, suggesting a dominant role for prostaglandins and leukotrienes in these manifestations. In the cytokine release phenotype in which IL-6, TNFa or IL-1b are released, premedication with paracetamol (acetaminophen), nonsteroidal anti-inflammatory agents or corticosteroids, together with a slow infusion rate, can generally prevent the reaction [19]. In this way, a "tailor-made" or personalized premedication according to the endotype, phenotype and biomarkers of the reaction could be design.

Regardless of whether there has been an HSR, all chemotherapy drugs and monoclonal drugs associate a standardized premedication to prevent adverse effects and HSR. Thus, platinum salts, which are very emitizing, are premedicated with dexamethasone associated with a serotonin inhibitor such as granisetron or substance P inhibitors such as aprepitant. In order to prevent HSR in the first and second cycle, taxanes are premedicated empirically with dexamethasone, antiH1 (dexchlorpheniramine)

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and antiH2 (ranitidine). mAbs are premedicated with hydrocortisone/methylprednisolone, dexchlorpheniramine/diphenhydramine and paracetamol.

Treatment of Reactions During Desensitization

Drug HSRs during desensitization can be of varying severity. Reactions can appear during the first phases of the procedure, as is the case of taxanes that induce non-IgE mediated reactions usually during the first or second administration [20]. However, it is more common for HSRs to occur during the later phases, as is the case of platinums which generally produce IgE-mediated reactions after 7th or 8th administrations [21].

When a reaction occurs, the administration of the drug should be stopped and the patient treated according to his/her symptoms. Only in the case of mild symptoms, it can be considered to continue with the administration of the drug and wait for them to resolve spontaneously or treat if they progress or do not resolve. Once the symptoms resolve, the desensitization protocol can be restarted in the same place where the reaction occurred, prolonging or not the time of the stage. In addition, intermediate stages can be introduced [17].

For subsequent desensitization's, the initial protocol must be modified. Depending on the moment in which the reaction with the previous desensitization occurred, different strategies can be established. Thus, if the reaction occurred in the initial stages of desensitization, it is recommended to start the regimen with a more dilute initial dose and if the reaction occurred in intermediate or final stages, intermediate steps can be added prior to the stage in which the symptoms occurred [17]. It is also possible to increase or modify the premedication or add medication in the stage immediately prior to that in which the reaction occurred [19].

These strategies are not exclusive and one or more can be used depending on each patient.The patient should always be counseled that desensitization is not a permanent cure, but a temporary one, so he should continue to report an allergy to that agent in the future.

Conflict of Interest Statement

Authors disclose no financial relationship with a pharmaceutical company, or laboratory products manufacturer for this study. We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal.

Conclusion

- Hypersensitivity reactions to chemotherapeutic agents and mAbs have increased in recent years, which implies an increase in the demand for care in allergy services.
- A diagnostic approach, based on the recognition of the clinical phenotypes, the underlying endotypes, and the evaluation of biomarkers, led us to the establishment of an initial desensitization protocol, with adjustments based on the patient's response.
- Molecular and cellular mechanisms of DS have yet to be clearly elucidated, but most research has focused on the role of mast cells and basophils.
- DS is a high-risk procedure, which must be individualized, assessing the risk / benefit of its performance in each patient.

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