



Management of adverse reactions induced by chemotherapy drugs

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Purpose of review

There is a broad spectrum of chemotherapy-induced adverse reactions. Hypersensitivity reactions are being extensively studied as they can affect the ideal treatment. The goal of this review is to describe the current management of adverse reactions to chemotherapy, focusing on hypersensitivity events.

Recent findings

The range of possible desensitization protocols is increasing, as well as the delabeling algorithms and diagnostic tools. One-bag desensitization protocols, omalizumab use in immediate hypersensitivity reactions, slow desensitization protocols in nonimmediate hypersensitivity reactions and standardization of skin tests for platinum drugs, are some examples.

Summary

The handling of adverse reactions to chemotherapy is evolving, with the increasing identification of hypersensitivity reactions and the development of strategies for their management, to maintain the culprit drug.

Keywords

chemotherapy, desensitization, diagnosis, drug allergy, hypersensitivity

INTRODUCTION

Adverse reactions to chemotherapy are a broad spectrum of manifestations that could be treated according to their severity, clinical presentations, as well as patient's comorbidities. Hypersensitivity reactions, whose prevalence is not well known, are the most studied adverse side effects, being desensitization procedures the paramount choice to manage them. However, the characteristics of each desensitization protocol can vary depending on the offending drug, and recent evidence points out that risk-assessment and delabeling tools could be other options. Recently, both the European Academy of Allergy and Clinical Immunology and the Spanish research network of Asthma, Adverse Drug Reactions and Allergy (ARADyAL) published consensus on the investigation of hypersensitivity reactions to chemotherapy [1^{*,2*}]. Therefore, this review will discuss the general handling of chemotherapy-induced adverse reactions, describing the most recent data on management of hypersensitivity events.

Most drugs produce multiple effects but usually only one – the therapeutic effect – is desired for the treatment of a disease. The other effects can be considered undesired, whether they are intrinsically harmful or not. Chemotherapeutics are notorious

for their common occurrence of adverse drug reactions (ADR), depending on the drug itself and dosage, mechanism of action, type and stage of cancer, that can occur in different organs and systems, with different stages of severity [3]. The analysis of 591 patients undergoing chemotherapy showed an incidence of 58.6%, of ADR more common in female individuals (73.6%) and in patients treated for breast cancer [4].

THE SPECTRUM OF ADVERSE DRUG REACTIONS TO CHEMOTHERAPY

The most frequently reported ADR to chemotherapy are type A, like fatigue, nausea and vomiting, diarrhea or constipation, myelosuppression, hair loss and skin lesions [3]. Fortunately, these ADR are

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KEY POINTS

- Chemotherapy-induced adverse reactions can vary from mild symptoms to life-threatening reactions.
- HSRs are the most well studied adverse effects, whose management is mainly through desensitization approach, showing efficacy in all ages.
- Beyond desensitization, the risk assessment as well as delabeling tools demonstrate usefulness in decreasing unnecessary desensitization protocols.
- Different desensitization protocols and use of premedication are reported in case series, although with scarce and nonstandardized data.

the expected ones and can be treated symptomatically, allowing the maintenance of the treatment. On the other hand, hypersensitivity reactions (HSRs) with a specific humoral and/or cellular immune component or basis, have been documented for most cancer chemotherapies, and although considered to be uncommon, their real incidence are not well known but they appear to be increasingly reported [5[•]].

Hypersensitivity reactions to chemotherapy

In the last decades, the study of HSRs to antineoplastic drugs has grown exponentially, as these reactions can jeopardize the ideal treatment of the patient. HSRs are more frequently caused by platinum salts (e.g. cisplatin, carboplatin, and oxaliplatin), taxanes (e.g. paclitaxel and docetaxel), L-asparaginase, and monoclonal antibodies (e.g. rituximab, infliximab, trastuzumab, bevacizumab, etc.) [6]. As these can be life-threatening reactions, they can represent a serious challenge in treating patients with the preferred or first-line therapies.

Recently, European Network on Drug Allergy and Drug Allergy Interest Group of the European Academy of Allergy and Clinical Immunology organized a task force to provide data and recommendations regarding HSRs in chemotherapy, focusing on its epidemiology, risk factors, type of the culprit drug, pathogenesis, clinical presentation, and diagnostic tools, as well as unmet needs in all of these topics [1^{••}]. Additionally, 16 allergy departments belonging to the Spanish research network of ARADyAL presented a review regarding this topic, describing phenotypes and endotypes of reactions to chemotherapy and providing general guidelines for the diagnosis and management of HSR in this field [2[•]].

MANAGEMENT OF ADVERSE DRUG REACTIONS

As previously referred, most common ADRs are treated symptomatically, allowing the patient to maintain the treatment of choice. However, in cases of neurological, cardiac, renal and other organ-specific toxicities, the decision to maintain or suspend the therapy will depend on the severity of these reactions and to the possibility of their control, as well as the balance of therapeutic benefit of treating the neoplastic disease with the offending drug.

In the presence of a potential chemotherapy-induced HSR, the clinician is placed in the unenviable position of verifying drug causality and weighing the risks of discontinuing therapy against the possibility of keeping it [1^{••},6]. In recent years, several strategies have been developed, allowing the treatment with first-line therapies that would not be possible otherwise.

Drug desensitization

Drug desensitization is the induction of a temporary drug tolerance, by delivering increasing amounts of it over hours to days [5[•]]. It is an extremely useful procedure enabling patients to safely receive a drug to which they previously had an HSR, and which is simultaneously the treatment of choice for that patient.

In recent years, different drug desensitization protocols have been developed, not only for immunoglobulin E (IgE)-mediated immediate hypersensitivity but also including non-IgE-mediated, nonimmunological, or delayed T-cell-mediated reactions [7,8,9^{••}].

Two categories of desensitization protocols are currently available: rapid drug desensitization (RDD), commonly used, in which full therapeutic doses can be reached in relatively short time, typically 4–12 h [5[•]], and slow drug desensitization (SDD), recommended for some restricted reactions of type IV delayed hypersensitivity reactions with T-cell involvement [7,8].

The Adverse Drug Reaction and Desensitization Program in Brigham and Women's Hospital is the worldwide establish protocol for RDD, in which the culprit drug solution (1 : 1) is diluted to 1 : 10, 1 : 100 and sometimes 1 : 1.000, and the concentration and rate of administration is escalated stepwise for 15 min [10]. This RDD is the most well studied procedure for the management of immediate reactions to chemotherapy, showing efficacy both in adults and children [5[•],11[•],12[•]].

Variations to this RDD protocol have been described, trying to decrease the number of steps

and/or the number of bags, keeping efficacy and safety [2^o,13]. A prospective study from Nishimura *et al.* used a four-step, 2 h carboplatin desensitization protocol, which was well tolerated and feasible in 14 chemotherapy sessions, after a risk-assessment analysis [14^o]. Moreover, a retrospective analysis comparing the outcomes of 109 patients undergoing 434 desensitizations using one-bag protocols (1BP) with 48 patients undergoing 205 RDD with a three-bag (3BP) protocol, found no significant differences in the severity of breakthrough reactions between the two protocols, with high completion rates for both the 1BP (432 of 434; 99.5%) and 3BP (204 of 205; 99.5%) [15^o].

The performance of SDD in chemotherapy is a matter of research as its procedures are not standardized [16^o]. Recently, a case series of five patients with a delayed skin rash after treatment with lenalidomide showed efficacy and tolerance to a 3-week SDD [16^o]. Moreover, patients with delayed hypersensitivity reactions can undergo RDD but reports of its efficacy are scarce. Eight patients referred to an Allergy Department with a delayed hypersensitivity reaction to chemotherapy performed RDD using a protocol with 8–13 steps, with temozolomide, bendamustine, gemcitabine, and docetaxel, within 4.6–6.5 h, with 13 breakthrough mild reactions reported but even though all patients completed their treatment [17^o].

The use of premedication in reactions to chemotherapy is still under discussion. A literature review regarding preventive premedication strategies in the prevention and management of hypersensitivity reactions to chemotherapy revealed that most premedication regimens including antihistamines, H2 antagonists, leukotriene receptor antagonists and corticosteroids have been derived empirically rather than determined through randomized trials [18^o]. Omalizumab, although not licensed as premedication or adjuvant therapy in chemotherapy desensitization protocols, revealed subservience as a premedication in RDD [19^o]. However, the published data present great heterogeneity between doses together with the interval between omalizumab injections and chemotherapy.

Risk assessment

The risk-assessment evaluation is mainly done by the allergist, considering desensitization procedures when no alternative options are available, or the culprit drug has far superior efficacy and the benefits of the culprit drug outweigh the risk.

The most important first step is taking a careful history (including underlying comorbidities and medication), physical examination and reviewing the details of the index reaction, including its

manifestations and the classification in terms of severity. Desensitization should be carefully applied in patients with significant risk factors for fatal breakthrough reactions, such as those with a history of severe HSR reactions as anaphylaxis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, those with cardiovascular or respiratory diseases, and those using beta-blockers [6,7].

Together with a risk assessment, delabeling procedures have been developed and include an allergy diagnostic workup, which would be discussed next.

Delabeling

Some authors advocate the performance of an allergy workup diagnosis prior to desensitization, reducing unnecessary protocols but keeping safety. The diagnostic tools include not only skin testing but also determination of total and specific IgE, tryptase, IL-6, basophil activation tests and drug provocation challenge [1^o,2^o].

Skin tests with the culprit drug can be a very useful diagnostic tool, with nonirritating concentrations already established for platinum, taxanes and L-asparaginase [1^o]. A single-center retrospective study included 21 patients who performed skin test with cisplatin, carboplatin and oxaliplatin, in which 11 patients showed a negative skin test for some or all platinum compounds, and after reintroducing treatment with the culprit drug, only one HSR was reported, showing a negative predictive value for skin test of 0.91 [20^o]. Skin test should be used judiciously in other situations as its concentrations are not standardized for other chemotherapy drugs, allowing the existence of false positives and false negatives [21].

Regarding serum measurements, platin-specific IgE is well documented for oxaliplatin and carboplatin, with sensitivity and specificity of at least 51 and 72%, respectively [1^o]. Data concerning the utility of specific IgE on other chemotherapies, as well as total IgE, is lacking. The basophil activation test (BAT) is a functional assay that measures the degree of basophil degranulation and CD63 expression following stimulation with allergen or controls by flow cytometry and correlates directly with histamine release [22]. Although chemotherapy can induce myelosuppression and toxicity to several cell lines, some cancer patients show activated circulating and tumor-infiltrating basophils that respond to IgE-mediated and non-IgE-mediated signals and could help identify hypersensitivity to therapeutic agents [23]. So, BAT could be a useful tool to detect an HSR in the absence of specific IgE, as well as a relevant biomarker of the outcome of RDD, mostly well studied to platinum compounds [24]. The profitability of BAT in taxanes' hypersensitivity was

described in a case report of a 50-year-old woman with a IgE-mediated hypersensitivity reaction after treatment with paclitaxel showed highly positive BAT, even at low allergen concentrations [25[■]], although we know, so far, that most reactions to taxanes are not IgE-mediated.

Meanwhile, IL-6 seems to be a good biomarker in cytokine release reactions, showing significant elevation of IL-6 during breakthrough reactions, correlated with fever, constitutional, cardiovascular, and neuromuscular symptoms [2[■],26[■]]. Finally, tryptase measurement is not only useful for studying the initial reaction but also during breakthrough reactions during desensitization and positive drug provocation challenges [1[■]].

The gold standard for studying HSR is the drug provocation test (DPT), which can rule out hypersensitivity in some cases, study patients who were receiving more than one drug simultaneously and to validate previous skin test results [1[■],2[■]]. In recent years, the working group led by Madrigal-Burgaleta have been carrying out DPT in cases where the risk is favorable according to a risk assessment firstly carried out, having so far demonstrated safety and leading to the reduction of unnecessary desensitization procedures [27[■],28[■]]. A 15-month pilot study conducted by Martí-Garrido *et al.* [27[■]] evaluated 93 patients with suspected HSR to chemotherapy and 23 DPT were performed in those who had a mild index reaction and negative skin test to the culprit drug (mainly platinum and taxanes), with only one positive DPT. A subsequent analysis for a 27-month period analyzed 187 patients, in which DPT were performed in 37, with almost all (34/37) showing negative DPT [28[■]].

CONCLUSION

HSR to chemotherapy are increasingly reported. Its management through desensitization procedures, risk assessment and delabeling strategies, is well documented. Some situations, in particular desensitization protocols with few or more than 12 steps and utility of premedication, need further research. Population-based studies evaluating the prevalence of HSR to chemotherapy, evaluation of the cost-effectiveness in using delabeling HSR to chemotherapy in addition to standardization of premedication regimen, are suggestions for future research.

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Conflicts of interest

Doctors Daniela Brandão Abreu has no conflict of interest to declare.

Josefina Rodrigues Cernadas has no conflict of interest to declare.

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- of special interest
- of outstanding interest

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This article describes how drug provocation testing with chemotherapy and biological agents can be implemented with good safety results. A 27-month retrospective period evaluated 187 patients with suspected hypersensitivity reaction to chemotherapy, in which DPT were performed in 37, with almost all (34/37) showing negative DPT.