Hypersensitivity Reactions To Chemotherapy: an EAACI Position Paper

Task Force Members: Mauro Pagani, Sevim Bavbek, Adile Berna Dursun, Patrizia Bonadonna, Josefina Cernadas, Emilio Alvarez-Cuesta, Ricardo Madrigal-Burgaleta, Sahar Hamadi, Soledad Sanchez Sanchez, Mariana Castells, Anca Chiriac

Pagani Mauro Medicine Ward C. Poma Mantova Hospital, Department of Medicine ASST Mantova Italy

Bavbek Sevim Division of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine Turkey

Alvarez-Cuesta Emilio Allergy Division, Ramon y Cajal University Hospital, Madrid, Spain.

Berna Dursun Adile Department of Immunology and Allergic Diseases, Recep Tayyip Erdoğan University, Rize, Turkey.

Bonadonna Patrizia Allergy Unit Azienda Ospedaliera di Verona Italy

Cernadas Josefina Department of Allergy and Clinical Immunology, Medical University, H. S. Joao, Porto, Portugal.

Chiriac Anca Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, Montpellier, France

Hamadi Sahar the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, USA

Madrigal-Burgaleta Ricardo Allergy & Severe Asthma Service, St Bartholomew's Hospital's, Barts Health NHS Trust, London, United Kingdom ORCID 0000-0002-3358-3578

Sanchez Sanchez Soledad Division of Allergy & Clinical Immunology, Department of Medicine, University Hospital Complex of A Coruna, A Coruna, Spain

Castells Mariana Division of Rheumatology, Immunology and Allergy, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston ORCID 0000-0001-6451-0163

ABSTRACT

Chemotherapeutic drugs have been widely used in the treatment of cancer disease for about 70 years and, even with the development of new therapies, they are still prescribed by oncologists, alone or in combination with other antineoplastic agents. All chemotherapies are able to provoke hypersensitivity reactions, even with different incidences, depending on the different class of these drugs, and these reactions are the third leading cause of fatal drug-induced anaphylaxis in the United States. In Europe deaths related to chemotherapy have also been reported. In particular, most reactions are provoked by platinum compounds, taxanes, epipodophyllotoxins and asparaginase. However, currently there are different points of view about the best procedures for the diagnosis, treatment and prevention of these reactions. Thus, the 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 the allergological work up in this field of drug hypersensitivity reactions. The aims of this position paper were to provide consensus on the investigation of HSRs to chemotherapeutic drugs and to give practical suggestions for clinicians that treat these patients, such as oncologists, allergologists and internists. Key sections cover: risk factors, pathogenesis, symptoms, role of skin tests, in vitro tests, indications and contraindications of drug provocation tests and desensitization of neoplastic patients with allergic reactions to chemotherapeutic drugs. Statements, recommendations and unmet needs were discussed and proposed at the end of each section.

Key words: chemotherapy, hypersensitivity reactions, allergy, drug hypersensitivity, desensitization, IgE-mediated reaction, drug provocation test, platinum compounds, taxanes.

BOX 1 Definitions and abbreviations

HSRs: Hypersensitivity reactions

CHT: Chemotherapy

DPT: Drug Provocation Test

ST: Skin tests

RDD: Rapid Drug Desensitization

RCHU: Ramon y Cajal University Hospital

SCARs: Severe Cutaneous Adverse Reactions

ACEI: angiotensin converting enzyme inhibitors

INTRODUCTION

Chemotherapeutic drugs have been used on the treatment of neoplasms since 1940s (1,2). Many types of anti-neoplastic agents were introduced in clinical practice and, despite the great diffusion of biological agents, chemotherapy (CHT) still represents the gold standard for the treatment of the majority of cancers, alone or in combination with the so-called more selective targeted-therapies, namely monoclonal antibodies or other biologicals (3). CHT can induce hypersensitivity reactions (HSRs) and are the third leading cause of fatal drug-induced anaphylaxis in the United States (4); Europe deaths-related to CHT have also been reported (5). The aims of this position paper were to provide consensus on the investigation of HSRs to chemotherapeutic drugs and to give practical suggestions for clinicians that treat these patients such as oncologists, allergologists and internists. Key sections in this paper cover risk factors, pathogenesis, symptoms and signs of reactions, role of skin tests, in vitro tests, indications and contraindications of drug provocations tests and desensitization of neoplastic patients with allergic reactions to CHT.

METHODS

This Position Paper was commissioned by the European Academy of Allergy and Clinical Immunology (EAACI). The task force group performed an intensive electronic literature search in MEDLINE, PubMed, databases of scientific societies, and reports of the AEMPS, European Medicines Agency, and the United States Food and Drug Administration by using the primary key words: hypersensitivity to chemotherapeutic drugs, hypersensitivity to antineoplastic agents, platinum compound hypersensitivity, taxanes hypersensitivity, skin test for chemotherapeutic drugs or the names of the class of drugs analysed in the position paper. However, the content of this Position Paper was restricted to allergy-like HSRs. Statements and unmet needs were carefully reviewed by the whole group and the quality of evidence and recommendations was discussed and graded by the Task Force members using the SIGN CRITERIA.

EPIDEMIOLOGY AND RISK FACTORS

The correct identification and diagnosis of hypersensitivity reactions to cytostatic drugs plays a crucial role in the treatment of patients with neoplasm, because unlike other drugs (eg, antibiotics) that may be easily replaced and exchanged in case of adverse reactions, chemotherapeutic drugs are often unique and essential for the treatment of the disease. Therefore, if a hypersensitivity reaction occurs, the physician has to decide between the benefit of continuing the treatment and the risk of a potential fatal anaphylactic reaction during the following administration of chemotherapy. Hence, the correct diagnosis of an allergic side effect to a cytostatic drug is crucial and cannot be postponed. Almost all chemotherapeutic drugs can induce HSRs and are reported in about 5% of patients even if this percentage is probably underestimated because oncologists do not often signal mild-moderate reactions, but only severe ones (6). It is possible to identify three categories of antineoplastic agents based on the frequency with which they cause hypersensitivity reactions, respectively drugs with high, moderate or low potentiality to determine HSRs (7). Therefore, the problem of HSRs is very significant for patients treated with the drugs included in the first group, represented by platinum compounds, taxanes, *L*-asparaginase, epipodophyllotoxins, while it is lower with others (8-16).

In studies with different design and aims, variables like atopy, previous HSRs to other drugs, age of patients, mastocytosis and type of cancer were inconsistent risk factors. Hereafter, we discuss some characteristics that have been identified and studied consistently enough to make them a reliable link in the management of such HSRs.

1- TAXANES

Risk factors of confirmed HSRs

Drug involved. Taxanes have a highly similar structure (docetaxel and cabazitaxel come from a common paclitaxel precursor) but differ by the solubilizer, i.e., Cremophor EL for paclitaxel, polysorbate 80 for docetaxel and cabazitaxel, respectively. Nanoparticule albumin-bound (nab-paclitaxel), devoid of Cremophor EL, seems to have a lower rate of HSRs (17), and it has been successfully used in several patients with previous anaphylactic reactions attributed to paclitaxel and docetaxel (18-20).

Previous history of HSRs to the same drug. The peculiarity of HSRs to taxanes is their occurrence at the 1st or 2nd infusion, and a common finding in many studies on taxane-induced HSRs is the decreasing risk of reaction with repeated exposures (21).

Reaction severity. In the largest study to date on allergy work-up to taxanes (21), patients with an immediate moderate to severe HSRs were significantly more likely to have positive Skin tests (ST) than patients with a nonimmediate or mild immediate HSRs

Risk factors for breakthrough reactions

Patients with negative ST and patients with a nonimmediate or mild immediate index reaction were significantly more likely to eventually resume regular infusion (21).

2- PLATINUM SALTS

Risk factors of confirmed HSRs

As for most HSRs, there is no association between atopy or HSRs to other drugs and HSRs to platinum salts (22-24).

Drug involved. Globally, all chemotherapeutic drugs showed a reduced risk of a confirmed HSR when compared to platinum compounds (24).

Previous history of HSR to the same drug. Patients with history of previous reactions to the same culprit-drug showed a 4-fold increased risk of HSR (25-27). The reaction becomes more severe at re-challenge.

Reaction severity. The initial reaction's severity does not seem to be predictive of a true HSR for some authors (22-24), while for others change in blood pressure and cardio-vascular involvement is a good clinical predictor. (25,26) Cutaneous symptoms (24,26,27) and presence of gastro-intestinal symptoms (24) were independently associated with an increased risk of confirmed HSR.

CHT schedule. One study suggested that patients receiving a repeat carboplatin regimen of 12 or more months after the first carboplatin regimen are at increased risk of HSRs, including severe ones (27), but others could not replicate this finding for this and other platinum salts (22,24,26,28).

Risk factors for breakthrough reactions

The main predictor for breakthrough reactions is a positive ST result (23,26).

3- ASPARAGINASE

Native E.coli asparaginase preparation, intravenous administration (29), a prolonged interval between different administrations of chemotherapy and the association with HLA DRB1 07:01 allele are the most important risk factors for the development of HSRs (30, 31).

Data about risk factors to epipodophyllotoxins are not available.

PATHOGENESIS

The pathomechanisms of HSRs to CHT has not yet been fully clarified.

PLATINUM COMPOUNDS

Platinum compounds (cisplatin, carboplatin, oxaliplatin) can frequently determine HSRs and are typically observed after multiple administrations. The development of hypersensitivity to several platinum agents is not well-understood but is thought to be related to type I IgE-mediated hypersensitivity. In fact: 1) the clinical pictures are similar to those of type I reactions; 2) prior exposure is necessary; 3) retreatment with the same platinum drug is the trigger to the immunological stimulation necessary for the reaction; 4) ST are often positive; 5) ST reactivity correlates with the risk of reaction during desensitization, 6) ST conversion from negative to positive is seen following re exposure and after development of reaction. (32). Also, specific IgE has been identified in patients who experienced HSRs to platinum agents. (24,33-35) Only anecdotal cases of delayed HSRs that are likely due to T-cell–mediated mechanisms are described. after platinum salts administration (36). Their clinical importance is not clear.

TAXANES

Paclitaxel and its solvent-free formulation nab-paclitaxel, docetaxel and cabazitaxel cause HSRs that usually (95%) develop during the first or second infusion with the most severe reactions occurring within the first few minutes. (21) Probably the majority of HSRs is provoked by the direct complement activation by cremophor EL and/or polysorbate, emulsifying agents added to the formulation of these drugs. However, in some cases an IgE-mediated mechanism had been postulated, based on the positivity of ST performed on patients with immediate reactions to taxanes (21). The appearance of reactions to the first exposure could be explained by the fact that taxanes molecules can be isolated from yew tree pollen, as well as from hazelnut trees and its nuts, providing potential sources of environmental exposure (37,38).

L-ASPARAGINASE

Asparaginase is derived from a bacterial polypeptide protease available in 3 forms. (6) Most HSRs occur during the first hour of administration even if delayed reactions have been reported (39). The mechanism responsible is not fully understood. There is evidence suggesting that HSR to asparaginase may be an IgE-mediated type I reaction, based on positivity of ST (40). Complement activation mediated by IgG or IgM may also be implicated (41).

EPIPODOPHYLLOTOXINS Epipodophyllotoxins, etoposide and teniposide are antimitotic agents used in several malignancies. HSRs usually occur after repeated exposure to the agents, although HSRs during first administration have been observed (42). Both immunologic and non-immunologic mechanisms can be implicated (43). Teniposide and intravenous etoposide are respectively dissolved in cremophor and polysorbate (Tween) 80. Oral etoposide is not associated with hypersensitivity reactions, suggesting that the solvent may be responsible.

Statements and recommendations

IgE-mediated reactions are responsible for some immediate, often severe HSRs to platinum compounds (Grade C)

The majority of HSRs to taxanes are determined by the direct activation of complement system by the drug. In some cases, however, IgE-mediated reactions have been observed (Grade C)

Epipodophyllotoxins HSRs are provoked either by immunologic and non-immunologic mechanisms (Grade D)

Unmet needs:

The exact role of specific IgE in HSRs to taxanes

CLINICAL PRESENTATION

Almost all chemotherapeutic agents have the potential to provoke HSRs that can be classified according to Brown's classification, in three grades of increasing severity (Table1).

Tab. 1: Severity grading system of immediate HSR.

Grade	Severity	Description
I	Mild	Symptoms are limited to the skin (e.g. flushing) or involve a single organ/system and are mild (e.g. mild cough)
II	Moderate	Symptoms involve at least 2 organs/systems (e.g. flushing and dyspnea), but there is no significant decrease in blood pressure or oxygen saturation
III	Severe	Severe symptoms typically involve at least 2 organs/systems, and there is a significant decrease in blood pressure (systolic <90 mm Hg and/or syncope) and/or oxygen saturation (<92%)

(44)

HSRs usually occur during or within a few hours after the end of drug infusion, although it is possible to observe nonimmediate reactions that appear afterwards by hours or days after the end of CHT administration (45). Cutaneous manifestations, such as flushing and/or pruritus, which can progress to urticaria, angioedema, and full body erythema are the most common symptoms; involvement of the respiratory and/or gastrointestinal tracts can follow the initial cutaneous symptoms. In severe cases, hypotension, cardiovascular collapse and even death occur (46, 47). Other less frequent non critical symptoms are represented by chills and fever such as seen with monoclonal antibodies, back and chest pain and hypertension, particularly with taxanes (Table 2).

Tab. 2. Symptoms of immediate reactions to chemotherapeutic drugs (48-56)

Skin and mucosa	Warmth, flushing, itching, urticaria, angioedema
Head and Neck	Ocular itching, hyperemia, tearing, periorbital edema,
	Nasal itching, rhinorrhea, nasal congestion, sneezing
	Itching or tingling of lips, tongue, oral mucosa, metallic taste, angioedema of lips, tongue, uvula
	Sense of swelling in the throat, change in voice, hoarseness, difficulty in swallowing, stridor
Respiratory	Dyspnea, chest tightness, cough, wheezing, cyanosis
Cardiovascular	Faintness/dizziness, palpitation, syncope/loss of consciousness, tunnel vision, hypotension, cardiac arrest
Gastrointestinal	Nausea, vomiting, abdominal cramp/pain, diarrhea
Gynecological	Vaginal itching, uterin cramp/bleeding, incontinence
Neurological	Anxiety, sense of impending doom, altered mental status, seizures
Others	Back and chest pain

SKIN TESTS

In presumed immune-mediated reactions, prick and intradermal tests performed to detect drug specific IgE are useful only for a few chemotherapeutic drugs, in particular platinum salts and probably for taxanes. In addition, reactions can be caused by drugs utilised for premedication such as steroids, or serotonin 5HT3 receptor antagonists. (57,58)

It's very important to underline that, before the administration of ST the allergologist has to wash hands thoroughly with soap and water and wear clean disposable gloves, the gown and mask or visor.

Regarding platinum compounds, ST is performed for:

1) Diagnosis
2) Prevention
3) Risk stratification
4) Evaluation of cross-reactivity

The best results are obtained when ST are performed in the interval ranging from 6 weeks to 6 months after the allergic reaction. (59)

As a diagnostic tool, carboplatin ST is positive up to 100% of patients in case of severe reactions, whereas the positivity in subjects with oxaliplatin hypersensitivity ranges from 26 to 100% (24,49). Data regarding ST with cisplatin are limited (60). Carboplatin ST has been investigated as a predictive tool for the development of HSRs in patients with recurrent gynecologicals cancer who required retreatment with carboplatin. They were seen to have a negative predictive value between 81% and 98,5% and a positive predictive value of 86% (61-63). Regarding oxaliplatin, a study demonstrated a negative predictive value of 95% (22). Therefore, ST for carboplatin and possibly oxaliplatin seem predictive of allergic reaction to these drugs; the tests should be performed on patients after 5 cycles of CHT especially when the therapy is re-administered more than 12 months after the last infusion.

ST with carboplatin and oxaliplatin are useful for risk stratification of patients who have experienced HSRs. In fact, patients with positive ST are more likely to experience HSRs during desensitization compared with patients with negative ST (50).

Cross-reactivity to other platinum-containing drugs can occur; in particular some reports describe severe HSRs to cisplatin and oxaliplatin in patients with previous allergic reactions to carboplatin. (62,63), but a recent paper had demonstrated a very low cross-reactivity between cisplatin and the other platinum salts. (64). Therefore, if it is not possible to utilize another class of chemotherapy, negative ST may be useful in selecting an alternative safe platinum agent. (60,64-67)

As far as taxanes are concerned, positive ST in patients with suspected HSRs to paclitaxel and docetaxel were reported by different authors, considering that at least in some cases, allergic reactions are IgE-mediated (21,68,69). There aren't experiences regarding ST with emulsifiyng agents included in the drugs formulations In regard to other chemotherapeutic drugs, ST proved positive in patients who reacted to cyclophosphamide, procarbazine, gemcitabine, metotrexate, and L-asparaginase but the diagnostic and predictive value of these results remains uncertain. (68-72)

Table 3 shows the non-irritating concentrations of ST for chemotherapeutic drugs

Tab.3: Non-irritating concentrations of ST for chemotherapy

Drug	Prick test dilutions (mg/mL)	Intradermal test dilutions (mg/mL)
Carboplatin	10	0.1 1
Oxaliplatin	5	0.05 0.5 5
Cisplatin	1	0.01 0.1 1
Paclitaxel	1 (6)	0.001 (0.006) 0.01 (0.06)
Docetaxel	4 (1)	0.04 (0.01) 0.4 (0.1)
L-Asparaginase	A drop of reconstitute 5000 KU	0.01 mL of reconstitute 5000 KU
Methotrexate	10	0,1 1 10
Procarbazine	5	0.05
Gemcitabine	38	0.0038 0.038

Statements and recommendations

ST is the most readily available diagnostic test (Grade B).
ST may be useful for the diagnosis of immediate IgE-mediated HSRs to platinum compounds (Grade B) and taxanes (C).
Intradermal test should be performed, as prick test is usually negative (Grade C).
ST for chemotheraputic drugs is also a safety procedure for patients with severe immediate reactions (Grade C).
ST concentration is well-standardized for platinum compounds and taxanes (Grade C).
ST is useful for the risk stratification of patients with HSRs to platinum compounds and taxanes (Grade C).
ST could be useful for the evaluation of cross-reactivity between drugs belonging to the same class (GRADE D).

Unmet needs:

Standardization of ST for chemotherapeutics drug other than platinum compounds and taxanes
Definition of the role of patch test

DRUG PROVOCATION TEST

The Drug Provocation Test (DPT) is the gold standard diagnostic technique used in the study of drug hypersensitivity reactions and involves the controlled administration of a drug (75). DPT is a helpful tool in the diagnosis of HSRs to CHT in order to rule out hypersensitivity in some patients, to study patients who receive more than one drug simultaneously, and as a Gold Standard to validate other diagnostic tests (24). However, published data on drug provocation testing with CHT are scarce.

In 2013 a pilot experience on the use of DPT for CHT agents was published (76). This experience was further validated in larger studies (23, 24), and DPT was found especially useful when more than one drug was involved (77). DPT can also be used to confirm tolerance to alternative cross-reactive drugs, for example to try different alternatives within the platinum salts family. (64).

Usefulness of DPT

Despite its inherent risks and the lack of universal standardization of optimal protocols for most drugs (78), DPT could prevent non-hypersensitive patients from unnecessary rapid drug desensitization (DS) procedures when it is systematically applied prior to DS. In fact, the Ramon y Cajal University Hospital (RCUH) study demonstrated that from 33% to 56% of all referred patients (depending on culprit drug) with unequivocal clinical history showed a negative DPT and therefore could avoid DS (24). See table 4.

DPT in practice

According to the vision of EAACI and RCUH (75), the following key point is paramount for a successful DPT implementation: a "safety first" policy. We cover this at length in the "therapeutical approach" section of this article (see below).

In the RCUH studies, 64% (58/91) (76) and 67% (229/341) (23) of all performed DPTs were negative and only 4% (4/91) (24) and 5% (17/341) (23) of all performed DPTs showed a severe reaction, according to Brown's classification (44). However low this percentage might be, these reactions are unpredictable and therefore patient selection must include a careful risk assessment. Moreover, the selected location should ideally include 1:1 nurse:patient ratio, intensive surveillance by expert personnel (including bedside physical presence of an allergist), continuous monitoring access to crash cart, and rapid access to Intensive Care Unit should a severe reaction occur. (Tab 5)

The optimal strategies for introducing systematic DPT in the study of hypersensitivity to CHT are still a matter of discussion and vary locally. (23,80-83). Contraindications for DPT should be the same as the general contraindications for DPT, (75) including the lack of access to adequate installations and/or to drug allergy expert personnel and/or to specific resources that ensure appropriate risk-management plans. Additionally, we should take into account the specific characteristics of these drugs and avoid DPT in patients who do not need any further treatment with the culprit antineoplastic drug or who are

going to change to an alternative (and equally effective) CHT schedule (23-25). Table 6 shows an example of DPT or drug challenge with oxaliplatin.

Table-4. Global results on drug provocation testing (DPT) from the largest studies including DPT with different antineoplastic agents.

DPTs	**Patients n = 156**	**Patients n = 515**
	Ref no:(24)	**Ref no: (23)**
Negative	58/156 (37%)	229/515 (45%)
Positive	33/156 (21%)	112/515 (22%)
Not undergone	65/156 (42%)	174/515 (34%)
Severity of the reaction (in DPT positive cases)	n = 33 (%)	n = 112 (%)
Grade 1	16/33 (48%)	48/112 (43%)
Grade 2	13/33 (39%)	47/112 (42%)
Grade 3	4/33 (12%)	17/112 (15%)

Legend: DPT, drug provocation test. It is of note that Pasteur et al. (64) used DPT as a diagnostic technique, both to rule out an allergy and to confirm tolerance to alternative platinum salts. The number of patients in which DPT was used to rule out an allergy to the culprit drug was small (n=16), but none of them were positive.

TABLE 5: Details on drug provocation testing (DPT) with chemotherapy agents as per Ramon y Cajal University Hospital (RCUH) protocol (23,24,79).

Timing	The patient's next scheduled treatment should be used for DPT, thus avoiding delays or overdose. This will depend on chemotherapy regimes, oncology/patient decisions, and individual patient treatments. If the elapsed time from the reaction is too short (<1month), skin testing and DPT could potentially be falsely negative. Thus, although data have not been published yet, the next chemotherapy session should also be supervised in those cases. Likewise, long elapsed time from reaction to testing might incur in false negatives.	
Dosage and number of steps	**Standard approach to DPT:**	Infusion under standard conditions. Protocol as per Manufacturer's Instructions and Institutional Recommendations. When these are not available, there are specific product information leaflets available at www.ema.europa.eu or products.mhra.gov.uk. These drugs are meant to be infused for long periods of times, so the dose/minute ratio is already low on standard infusion.
	Cautious approach to DPT:	In patients with severe initial reactions, very immediate rapid-onset reactions, or higher risk assessments, a more cautious approach to DPT might be starting at 1/4 or even 1/8 dose/minute of the standard dose and progressively increasing to 1/1 in a step-wise manner every 30 minutes. But, a "cautious approach DPT" could potentially induce tolerance (false negatives). Thus, we suggest that patients not reacting to a "cautious approach DPT" should undergo a "standard approach DPT" for their next chemotherapy session, to confirm tolerance before being discharged to standard care..
	Precautions	Some authors recommend stopping beta-blockers and ACE inhibitors before the procedure. The evidence for this is controversial and stopping these drugs is not free from other risks. This should be a local decision.
	Intensified premedications	Not recommended as they can help to induce a false temporary tolerance (therefore defeating the whole purpose of DPT) or they can hide warning symptoms of a reaction (therefore compromising safety).
	Chemotherapy regime	To keep standard regimes unaltered, additional required medications (other antineoplastics, leucovorin, etc.) should be also administered, as prescribed by the referring physician.
	DPTs with concomitant drugs	Whenever needed, DPT with other non-cytotoxic drugs such as premedication, concomitant drugs possibly involved in the initial reactions should be performed before the DPT with the culprit-drug. If more than one chemotherapeutic drug is possibly involved in an immediate DHR, and they need to be administered in the same day (consultation with oncologist needed). These DPTs could be performed on the same day, but both drugs should be separated as much as possible. When the initial DHR is a delayed one, separation needs to be recommended to ensure a rapid and certain diagnosis.
Blinding	Simple blind DPTs may be necessary when it is suspected that symptoms suffered by the patient may be of psychological origin or may be caused by other conditions mimicking anaphylaxis. Blind DPTs with placebo have to ideally be programmed on the same day and right before the standard DPT so as not to alter standard regime scheduling.	
Results	Drug provocation test is considered positive when it reproduced the original symptoms or showed an objective DHR	
Restart protocol	It is paramount that the patient does not miss or alter their chemotherapy regimes in order to perform a DPT. Therefore, in case of a positive DPT, once symptoms are controlled after adequate treatment and the patient is asymptomatic, the infusion may be immediately (approximately within 30 min after the DHR) restarted at 1/4 of the final infusion rate for 15 min,, and then increased to 1/2 of the initial infusion rate until all the medication is administered ('restart protocol'). A phenomenon of temporary tolerance after the positive DPT reaction allows patients to safely receive the remaining treatment.	

Follow up	Patients with a negative DPT are eligible to continue with standard administrations. But, some patients, especially platin-reactive patients, may need follow-up during the next administrations, including preventive ST. Platin-reactive patients, in whom a period longer than 6 months has passed between initial reaction and allergy workup, are suspected to be experiencing a negativization of ST, and may be experiencing resensitization, similar to what has been observed with betalactams. Therefore, in these patients, one approach may be to retest after the first negative DPT, by administering the following platin session under DPT conditions and after repeating ST.
"Uncontrolled" DPTs	"Uncontrolled DPTs" (i.e., administering a culprit-drug or a cross-reactive drug to a reactive patient lacking allergy/risk assessment, in inappropriate environments, by untrained and/or unaware personnel) are common. These practices must be emphatically discouraged and institutionally blocked, to ensure patient's safety. These practices may entail unnecessary risks, may even account for deaths, and may result in the missing of many important data. Multidisciplinary institutional teams lead by allergists are the key for avoiding these risks.

Table 6. Example of a drug provocation test or drug challenge with oxaliplatin as per the Ramon y Cajal University Hospital (RCUH) standard and cautious protocols based on the officially available product information by the European Medicines Agency (EMA) for a total dose of 200 mg of oxaliplatin that was intended to be administered in 500 ml and in 2 hours.

Standard approach to drug provocation test:

Total dose	200 mg		Solution concentration		Drug	
Solution A	500 ml		0.4 mg/ml		Oxaliplatin	
Step	Solution	Rate (ml/h)	Administered volume (ml)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	250	500	120	200	200

Cautious approach to drug provocation test:

Total dose	200 mg		Solution concentration		Drug	
Solution A	500 ml		0.4 mg/ml		Oxaliplatin	
Step	Solution	Rate (ml/h)	Administered volume (ml)	Time (min)	Administered dose (mg)	Cumulative dose infused (mg)
1	A	60	30	30	12	12
2	A	120	60	30	24	36
3	A	250	410	98.4	164	200

LEGEND:

The recommended concentrations and rates for oxaliplatin are rather wide (between 0.2 and 0.7 mg/ml to be administered 2-6 hours), and so concentrations and infusion times need to be discussed according to local guidelines. Always check product information leaflets and local protocols for specific administration recommendations in specific populations. Only use premedication as per manufacturer's instructions. Using additional premedication for drug provocation testing is not recommended, as it can alter tolerance and hide warning symptoms. Drug provocation testing is a high-risk and high-complexity technique, and it should only be performed by expert allergists in dedicated spaces.

Product information leaflets are freely available for all products either from their manufacturers, or at nationwide official websites such as www.ema.europa.eu, or products.mhra.gov.uk. For further information on drug challenge or drug provocation test, see table 5.

Statements and recommendations

- DPT is the Gold Standard for the diagnosis of HSRs to drugs (Grade A).
- DPT prevents a significant number of patients from unnecessary drug desensitizations. (Grade B).
- DPT has a good safety profile when performed in specialist centers (Grade B).
- DPT is a high-risk technique and benefits from dedicated spaces and expert personnel (Grade B).

Unmet Needs:

- Standardization of protocols and selection of candidates, whilst acknowledging valid local variations.
- Multicenter studies and identification of differences in populations.

IN VITRO TESTS

Specific IgE

There is only one case of reported specific IgE for taxanes; (8) however, this technique has been widely and successfully used for platins. Early pilot studies showed clear data on the benefits of implementing specific IgE for the study of reactions to platins (33,76); See table 7.

In 2015, oxaliplatin-specific IgE was validated in a prospective study with DPT regardless of sIgE results (24). The authors concluded that both positive ST and oxaliplatin-specific IgE are good tools to confirm oxaliplatin hypersensitivity, but negative results are less useful (24). These conclusions match those of other experiences with ST and sIgE for the study of drug allergy (80).

- Basophil activation testing (BAT) as a diagnostic tool in chemotherapy has only been used in a limited number of cases with platins (85,86).
- Tryptase determination is a widely available biomarker for anaphylaxis (both IgE-dependent or non-IgE-dependent). Despite its limitations, it is useful when comparing serum baseline tryptase with tryptase during a reaction. This is applicable for the study of the initial reaction, but also during a positive DPT or a reactive RDDs, for better endotyping and tailored planning (25,33,87).

Statements and recommendations:

In vitro detection of specific IgE for platinum compounds is a useful tool for diagnosis of HSRs to these drugs (GRADE B)

Unmet needs

Identification of new and more efficient biomarkers

Standardization/validation of BAT for chemotherapeutics

Evaluation of the role of total IgE as a predictive factor of HSRs

Tab 7: Comparison of diagnostic indexes as assessed in the largest reported series of platin-specific IgE.

	CUTOFF POINT 0.10 (95% CI)	CUTOFF POINT 0.35 (95% CI)
OXALIPLATIN-SPECIFIC IgE		
Madrigal-Burgaleta et al. (76), prospective cohort of 23 oxaliplatin-reactive patients: results from 16 oxaliplatin-reactive well-characterised patients (diagnosed as positive or negative after a protocol including ST and DPT regardless of the specific IgE results).		
Sensitivity	54%	38%
Specificity	100%	100%
Caiado et al. (33), results from a retrospective study with 12 controls, and 12 cases (10 oxaliplatin-reactive patients with positive ST and 2 oxaliplatin-reactive patients with a diagnosis based on clinical history).		
Sensitivity	75%	
Specificity	75%	
Positive Predictive Value	75%	
Negative Predictive Value	75%	
Alvarez-Cuesta et al. (24), prospective cohort of 74 oxaliplatin-reactive patients: results from 64 oxaliplatin-reactive well characterised patients (diagnosed as positive or negative after a protocol including ST and DPT regardless of the specific IgE results).		
Sensitivity	51% (37 - 65)	34% (29.9 - 47.1)
Specificity	71.9% (56.3 - 87.5)	90.3% (79.7 - 100)
Positive Predictive Value	73.5% (58.7 - 88.4)	85% (69.4 - 100)
Negative Predictive Value	48.9% (34.6 - 63.2)	45.9% (33.4 - 58.4)
Likelihood ratio +	1.8 (1.0 - 3.4)	3.5 (1.1 - 11.0)
Likelihood ratio -	0.7 (0.5 - 1.0)	0.7 (0.6 - 0.9)
CARBOPLATIN-SPECIFIC IgE		
Caiado et al. (33), results from a retrospective study with 5 controls, and 12 cases (12 carboplatin-reactive patients with positive ST).		
Sensitivity	75%	
Specificity	75%	
Positive Predictive Value	75%	
Negative Predictive Value	75%	

LEGEND: CL: confidence interval, ST: skin testing; DPT, drug provocation test
CI: confidence interval; ST, skin testing; DPT, drug provocation testing.

THERAPEUTICAL APPROACH

Initial reaction and RDD programs

Allergists rarely witness initial reactions, as they usually occur in oncology settings or outpatient clinics. Thus, the fundamental role of the allergist in this setting is to lead an institutional multidisciplinary collaboration so as to satisfactorily manage these highly complex patients. Specific institutional programs for RDD, led by expert allergists, are known to be a successful approach for hypersensitivity to chemotherapy agents in the 21st century, and many original articles show excellent results on the progressively outstanding performance of RDD programs and their achievements in local applications and improvements (15,21,25,37,75-77,85,88-90).

General therapeutical approach

The first step should be to make use of specific tools to classify the patient. We have discussed separately the available in vivo and in vitro techniques and current knowledge on their usefulness. Additionally, we have discussed the value of DPT, the diagnostic criterion standard.

Patient empowerment: Patients need to make decisions on their conditions based on two fundamental issues, namely (i) the indication of treatment by the Oncologist, and (ii) the risk assessment by the Allergist.

Risk assessment may vary locally, but it must be based on a "safety first policy". This safety first policy may only be guaranteed if these three fundamental pillars are present: (i) access to appropriate facilities and specific resources; (ii) locally designed risk management strategies open to tailored plans based on individual assessment, phenotyping and endotyping; and, (iii) access to expert personnel capable of appropriate patient selection and management provided the two previous pillars are met.

PREMEDICATION

Premedication is said to be effective and has been recommended for the prevention of hypersensitivity reactions to different chemotherapeutics, such as epipodophillotoxins and pegasparaginase (91). In addition, this procedure has dramatically decreased the incidence of HSRs to taxanes to 2-4% of cases, even if in last few years the incidence of reactions has increased to 10% (69), Premedication resulted ineffective in preventing true, IgE-mediated allergic reactions to platinum salts (92,93).Moreover, administering systematic premedication with corticosteroids and antihistamines had no significant effect on the effectiveness or safety of RDD in patients with confirmed hypersensitivity to paclitaxel (94).

Statements and recommendations

- Premedication with steroids and antihistamines (dexametasone 20 mg and chlorpheniramine 10 mg intravenous 1 hour before chemotherapy) is effective for the prevention of moderate and severe HSRs to taxanes (GRADE B).
- Premedication with steroids and antihistamines is effective for the prevention of HSRs to epipodophyllotoxins, asparaginase and doxorubicin (GRADE D).
- Premedication is not effective in case of true IgE-mediated HSRs (GRADE D).

DESENSITIZATION:

Principles and Practices of Desensitization

RDD is a therapeutic approach delivered through protocols to patients in need of first line drug therapy (95). It safely administers the needed medication and provides a temporary tolerance to drugs to which patients have presented immediate reactions to, including anaphylaxis and delayed reactions non-Severe Cutanous Adverse Reactions (SCARs). DS protects from severe reactions and allows the patients to receive the desired medication within minutes to hours, thereby preventing further delays in treatment for critically ill patients. (94) The principles of IgE RDD are based on in vitro and in vivo mast cell models. (96-99)

Desensitization candidates

Risk stratification is a critical part of DS qualification and success (Table 7).

Low-risk patients have presented a Grade I or II HSR with positive/negative ST. These patients do not have comorbidities and are not treated with β-blockers or/and angiotensin converting enzyme inhibitors (ACEI).

High-risk patients have presented a Grade III HSR and positive ST when it was available. High-risk patients include patients that are being treated with β-blockers or/and angiotensin converting enzyme inhibitors, as well as those patients who have mastocytosis, respiratory pathologies as cystic fibrosis, and cardiac pathologies, such as coronary disease . Pregnant patients are classified as high-risk.

Tab 8. Risk Stratification for RDD*:*

LOW RISK	HIGH RISK
Grade I or II HSR	Grade III HSR
ST +/-	ST +
No comorbidities	Comorbidities (cystic fibrosis, mastocytosis, HTA, coronary disease)
No β-blockers No angiotensin converting enzyme inhibitors (ACEI)	β-blockers ACEI
No pregnancy	Pregnancy

Candidate patients for RDD will include patients who have had a type I, cytokine-release syndrome, mixed reactions or a Type IV HSR, excluding SCARs, such as Steven-Johnson syndrome, toxic epidermal necrolysis, drug-related eosinophilia with systemic symptoms, acute generalized

exanthematous pustolosis. Serum sickness is not an indication for RDD. Upon the occurrence of a HSR, a tryptase level should be drawn 30 minutes after the initial symptoms, ST should be done 4-6 weeks after the HSR when available and BAT should also be evaluated when skin test is negative and BAT is available. It should be emphasized that RDD should only be performed when there is no alternative therapy.

The results of the previous tests should be used as a diagnostic tool to interpret whether a challenge or DS should be performed and to guide risk stratification.

If the test results are negative and the initial HSR is Grade I (low risk), a challenge may be performed. If there is no reaction during the challenge, the patient can be sent back to regular infusion. However, if there is a reaction, a tryptase level should be drawn and DS should be performed for the next drug exposure.

If the test results are negative and the initial HSR is Grade II/III (moderate-high risk), DS is indicated.

DS should always be performed in patients with positive skin tests, regardless of the grade of the initial HSRs, since IgE and mast cells are involved in the reaction and the risk of anaphylaxis is present at each re-exposure. (4)

Health care costs and efficacy

It has been hypothesized that the health care costs outweigh the benefits of RDD and that the long-term impact on drug efficacy is unknown because RDD protocols differ from standard administration. A recent report about safety, cost and efficacy of RDD has revealed that the overall costs of RDD are similar to standard administration and that drug efficacy is preserved with RDD. In this report, a tendency for increased life expectancy in carboplatin desensitized women was seen, although it did not reach statistical significance. (100)

Most RDD to chemotherapies (platins/taxanes) are uneventful. However, if a reaction were to occur, it would be during the 1st or the 2nd RDD. When a standard 3-bag protocol is performed, 75 % of the reactions occur within the last bag, with 50% of the reactions during the last step. Additionally, these reactions are generally less severe than the initial HSR. (25)

Fig.1 shows a decisional algorithm in patients with HSRs to chemotherapeutic drugs.

Statements and Recommendations:

RDD allows patients with HSRs to receive desired medication within minutes to hours (GRADE A).

RDD are indicated in patients with immediate reactions, anaphylaxis and delayed reactions non-SCARs (GRADE B).

RDD prevents the release of granule mediators by mast cells (GRADE B).

RDD has a very good safety profile when performed in specialized centers (GRADE B).

-Standardized protocols of RDD are available for the different chemotherapeutic drugs (GRADE C).

Unmet needs

Multicenter studies with particular regard to life expectancy in desensitized patients.
Type IV HSR, excluding SCARs are candidates for RDD

CONCLUSIONS

Currently, there are not a lot of data and research on the diagnosis and treatment of neoplastic patients with HSRs to chemotherapy. By summarizing actual knowledge in this field, the current document tries to give clinical recommendations for the best management of these infrequent but very important conditions involving patients with very severe diseases. The occurrence of HSRs to chemotherapeutic drugs implies a multidisciplinary approach among allergists, oncologists and internists is mandatory. Similarly, international cooperation between centres and specialists with expertise in this field is needed.

REFERENCES

1. World Health Organization available on www.who.int/health-topics/cancer

2. Goodman LS, Wintrobe MM, Dameshek W, Goodman MJ GilmanA, McLellan MJ. Landmark article Sept. 21, 1946: Nitrogen mustard therapy. Use of methyl-bis(beta-chloroethyl)amine hydrochloride and tris(beta-chloroethyl)amine hydrochloride for Hodgkin's disease, lymphosarcoma, leukemia and certain allied and miscellaneous disorders. By Louis S. Goodman, Maxwell M. Wintrobe, William Dameshek, Morton J. Goodman, Alfred Gilman and Margaret T. McLennan. JAMA. 1984 ;251:2255-61

3. De Vita Junior VT, Lawrence TS, Rosenberg SA: Principles and practice of Oncology 11th edition 2018; cap 20 Wolter Kluver Health Editor

4. Jerschow E, Lin RY, Scaperotti MM, McGinn AP. Fatal anaphylaxis in the United States, 1999-2010: temporal patterns and demographic associations. J Allergy Clin Immunol 2014;134:1318-28.e7.

5. RibeiroVaz I, Marques J, Demoly P , Polonia J, Gomes ER. Eur J Clin Pharmacol 2013;69:673-81.

6. Syrigou E, Syrigos K, Saif MW. Hypersensitivity reactions to oxaliplatin and other antineoplastic agents. Curr Allergy Asthma Rep 2008;8:56-62.

7. Pagani M The complex clinical picture of presumably allergic side effects cytostatic drugs: symptoms, pathomechanisms, reexposure and desensitization. Med Clin N Am 2010;94:835-852

8. 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;19:460-5

9. Markman M, Kennedy A, Webster K, Elson P, Peterson G, Kulp B, Belinson J. Clinical features of hypersensitivity reactions to carboplatin. J Clin Oncol. 1999;17(:1141.

10. Schiavetti A, Varrasso G, Maurizi P, Castello MA. Hypersensitivity to carboplatin in children. Med Pediatr Oncol 1999;32:183-5

11. 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. pii: 207084.

12 Baldo BA, Pagani M Adverse events to non-targeted and targeted chemotherapeutic agents. Emphasis on hypersensitivity responses Immunol Allergy Clin N Am 2014;34:565-596

13. Rowinsky EK, Donehower RC. Paclitaxel (Taxol). N Engl J Med 1995;332:1004–14.

14. Mertens WC, Eisenhauer EA, Jolivet J Ernst S, Moore M, Muldal A. Docetaxel in advanced renal carcinoma. A phase II trial of the National Cancer Institute of Canada Clinical Trials Group. Ann Oncol 1994;5:185-7

15. Kintzel PE. Prophylaxis for paclitaxel hypersensitivity reactions. Ann Pharmacother 2001;30:367–71.

16 Lee C, Gianos M, Klausermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. Ann Allergy Asthma Immunol 2009; 102: 179-87.

17) Pellegrino B, Boggiani D, Tommasi C, Palli D, Musolino A. Nab-paclitaxel after docetaxel hypersensitivity reaction: case report and literature review.Acta Biomed. 2017;88:329-333

18) de Leon MC, Bolla S, Greene B, Hutchinson L, Del Priore G. Successful treatment with nab-paclitaxel after hypersensitivity reaction to paclitaxel and docetaxel. Gynecol Oncol Case Rep. 2013 ;5:70-1.

19) Kimura K, Tanaka S, Iwamoto M, Fujioka H, Takahashi Y, Sato N et al Safety of nanoparticle albumin-bound paclitaxel administered to breast cancer patients with clinical contraindications to paclitaxel or docetaxel: Four case reports. Oncol Lett. 2013;6:881-884

20) Kloover JS, den Bakker MA, Gelderblom H, van Meerbeeck JP. Fatal outcome of a hypersensitivity reaction to paclitaxel: a critical review of premedication regimens. Br J Cancer. 2004;90:304-5.

21) Picard M, Pur L, Caiado J, Giavina-Bianchi P, Galvão VR, Berlin ST, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. J Allergy Clin Immunol 2016;137:1154–64

22) Pagani M, Bonadonna P Skin test protocol for the prevention of hypersensitivity reactions to oxaliplatin Anticancer Res. 2014;34:537-40.

23) Madrigal-Burgaleta R, Bernal-Rubio L, Berges-Gimeno MP, Carpio-Escalona LV, Gehlhaar P, Alvarez-Cuesta E. A Large Single-Hospital Experience Using Drug Provocation Testing and Rapid Drug Desensitization in Hypersensitivity to Antineoplastic and Biological Agents.J Allergy Clin Immunol Pract. 2019;7:618-632.

24) Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Ureña-Tavera A, Zamora-Verduga M, Lopez-Gonzalez P, et al. Delving into cornerstones of hypersensitivity to antineoplastic and biological agents: value of diagnostic tools prior to desensitization. Allergy 2015;70:784–94.

25) Castells MC, Tennant NM, Sloane DE, Ida Hsu F, Barrett NA, Hong DI et al. Hypersensitivity reactions reactions to chemotherapy: Outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574–580.

26) Wang AL, Patil SU, Long AA, Banerji A. Risk-stratification protocol for carboplatin and oxaliplatin hypersensitivity: repeat skin testing to identify drug allergy. Ann Allergy Asthma Immunol. 2015;115:422-8

27) Schwartz JR, Bandera C, Bradley A, Brard L, Legare R, Granai CO, Dizon DS. Does the platinum-free interval predict the incidence or severity of hypersensitivity reactions to carboplatin? The experience from Women and Infants' Hospital. Gynecol Oncol. 2007;105:81-3

28) Okayama T, Ishikawa T, Sugatani K, Yoshida N, Kokura S, Matsuda K et al Hypersensitivity Reactions to Oxaliplatin: Identifying the Risk Factors and Judging the Efficacy of a Desensitization Protocol. Clin Ther. 2015;37:1259-69.

29) Hasan H, Shaikh OM, Rassekh SR, Howard AF, Goddart K. Comparison of hypersensitivity rates to intravenous and intramuscular PEG-asparaginase in children with acute lymphoblastic leukemia: A meta-analysis and systematic review. Pediatr Blood Cance. 2017 J;64:81-88.

30) Burke M.J. How to manage asparaginase hypersensitivity in acute lymphoblastic leukemia. Future Oncol 2014;10:2615-2627

31) Kadoyama K, Kuwahara A, Yamamori M, Brown JB, Sakaeda T, Okuno Y. Hypersensitivity reactions to anticancer agents: data mining of the public version of the FDA adverse event reporting system, AERS. J Exp Clin Cancer Res 2011 30:93-98

32) Caiado J, Castells M. Presentation and diagnosis of hypersensitivity to platinum drugs. Curr Allergy Asthma Rep 2015 15:15-20. doi:10.1007/s11882-015-0515-3

33) Caiado J, Venemalm L, Pereira-Santos MC, Costa L, Barbosa MP, Castells M. Carboplatin-, Oxaliplatin-, and Cisplatin–specific IgE: Cross-reactivity and Value in the Diagnosis of Carboplatin and Oxaliplatin Allergy. J Allergy Clin Immunol Pract. 2013;1(5):494–500.

34) Pagani M, Venemalm L, Bonnadona P, Vescovi PP, Botelho C, Cernadas JR. An Experimental Biological Test to Diagnose Hypersensitivity Reactions to Carboplatin: New Horizons for an Old Problem. Jpn J Clin Oncol. 2012 ;42:347–50.

35) Brault F, Waton J, Poreaux C, Schmutz JL, Barbaud A. Hypersensitivity to platinum salts and taxanes: the value of skin tests and tolerance induction procedures. Ann Dermatol Venereol. 2017;144):685-695

36) Calvo M, De Barrio J, Sainz S, Infante P, Tornero ML Delayed cutaneous eruption to platinum salts chemotherapy J Allergy Clin Immunol 2004;113:S309

37) Feldweg AM, Lee C-W, 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;96:824–9

38) Dizon D.S. Schwartz J. Rojan A. Miller J. Pires L. Disilvestro P. et al. Cross-sensitivity between paclitaxel and docetaxel in a women's cancers program. Gynecol. Oncol., 2006;100:149-151.

39) Browne E, Moore C, Lu Z, Sykes A, Jeha S, et al Characteristics of Intravenous PEG-Asparaginase Hypersensitivity Reactions in Patients Undergoing Treatment for Acute Lymphoblastic Leukemia J Pediatr Oncol Nurs 2018;35:103-109

40) Galindo-Rodríguez G, Jaime-Pérez JC, Salinas-Carmona MC, Gonzales-Diaz SN, Castro-Corona A, Cavazos-Gonzales R et al. Do immunoglobulin G and immunoglobulin E anti-l-asparaginase antibodies have distinct implications in children with acute lymphoblastic leukemia? A cross-sectional study. Rev Bras Hematol Hemoter. 2017;39:202-209

41) Narta UK, Kanwar SS, Azmi W. Pharmacological and clinical evaluation of L-asparaginase in the treatment of leukemia. Crit Rev Oncol Hematol 2007;61:208–215

42) Lee, C.; Gianos, M.; Klaustermeyer, W.B. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. Ann Allergy Asthma Immunol 2009;102:179-187.

43) Sambavisan K, Mahmoud S, Kokache A, Seckl M, Savage P et al Hypersensitivity reactions to etoposide phosphate J Oncol Pharm Pract 2014;20:158-160

44) Brown S.G.: Clinical features and severity grading of anaphylaxis. J Allergy Clin Immunol 2004; 114:371-376

45) Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. Drug Saf 2001;24:767–79

46) Giavina-Bianchi P, Patil SU, Banerji A. Immediate hypersensitivity reaction to chemotherapeutic agents. J Allergy Clin Immunol Pract 2017;5:593-9.

47) Castells MC. Anaphylaxis to chemotherapy and monoclonal antibodies. Immunol Allergy Clin N Am 2015;35:335-348.

48) Navo M, Kunthur A, Badell ML, et al. Evaluation of the incidence of carboplatin hypersensitivity reactions in cancer patients. Gynecol Oncol 2006;103:608-13.

49) Otani IM, Wong J, Banerji A. Platinum chemotherapy hypersensitivity. Prevalence and management. Immunol Allergy Clin N Am 2017;37:663-77.

50) Wong JT, Lİng M, Patil S, et al. Oxaliplatin hypersensitivity: evaluation, implications of skin testing and desensitization. J Allergy Clin Immunol Pract 2014;2:40-5.

51) Maindrault-Goebel F, Andre T, Tournigand C, et al. Allergic-type reactions to oxaliplatin: retrospective analysis of 42 patients. Eur J Cancer 2005;41:2262-7.

52) Moon DH, Lee JM, Noonan Am, et al. Deleterious BRCA1/2 mutation is an independent risk factor for carboplatin hypersensitivity reactions. Br J Cancer 2013;109:1072-8.

53) Giavina-Bianchi P, Patil SU, Banerji A. Immediate hypersensitivity reaction to chemotherapeutic agents. J Allergy Clin Immunol Pract 2017;5:593-9.

54) Lazzareschi I, Ruggiero A, Ricardi R, et al. Hypersensitivity reactions to carboplatin in children. J Neuroncol 2002;58:33-7.

55) Picard M. Management of hypersensitivity reactions to taxanes. Immunol Allergy Clin N Am 2017; 37:679-93.

56) Feldweg AM, Lee CW, Matulonis UA, et al. Rapid desensitization for hypersensitivity reactions to paclitaxel and docetaxel: a new standard protocol used in 77 successful treatments. Gynecol Oncol 2005;96:824-9.

57) Iammatteo M, Keskin T, Jerschow E Evaluation of periprocedural hypersensitivity reactions Ann Allergy Sthma Immunol 2017;119:349-355.e2

58) Rutkowsky K, Wagner A, Rutkowsky K Immediate hypersensitivity reactions to steroids and steroid containing medications Curr opin Allergy Clin Immunol 2020;20:362-366)

59) Patil SU, Long AA, Ling M, Wilson MT, Hesterberg P, Wong JT, Banerji A. A protocol for risk stratification of patients with carboplatin-induced hypersensitivity reactions. J Allergy Clin Immunol. 2012;129):443-7

60) Leguy-Seguin V, Jolimoy G, Coudert B, Pernot C, Dalac S, Vabres P, Collet E. Diagnostic and predictive value of skin testing in platinum salt hypersensitivity. J Allergy Clin Immunol. 2007 ;119:726-30.

61) Markman M, Zanotti K, Peterson G, Webster K, Belinson J. Expanded experience with an intradermal skin test to predict for the presence or absence of carboplatin hypersensitivity. J Clin Oncol. 2003;21:4611-4.60) McAlpine JN, Kelly MG, O'malley DM Azodi M, Coombe K, Schwartz PE, Rutherford TJ. Atypical presentations of carboplatin hypersensitivity reactions: characterization and management in patients with gynecologic malignancies. Gynecol Oncol. 2007;105:211-7.

62) Gomez R, Harter P, Lück HJ Traut A, Kommoss S, Kandel M, du Bois A. Carboplatin hypersensitivity: does introduction of skin test and desensitization reliably predict and avoid the problem? A prospective single-center study. Int J Gynecol Cancer. 2009;19:1284-7.

63) Callahan MB, Lachance JA, Stone RL, Kelsey J, Rice LW, Jazaeri AA. Use of cisplatin without desensitization after carboplatin hypersensitivity reaction in epithelial ovarian and primary peritoneal cancer. Am J Obstet Gynecol. 2007;197:199.e1-4

64) Pasteur J, Favier L, Pernot C, Guerriaud M, Bernigaud C, Lepage C et al Low cross-reactivity between cisplatin and other platinum salts. J Allergy Clin Immunol: In Pract. 2019;7:1894-900

65) Dizon DS, Sabbatini PJ, Aghajanian C, Hensley ML, Spriggs DR. Analysis of patients with epithelial ovarian cancer or fallopian tube carcinoma retreated with cisplatin after the development of a carboplatin allergy. Gynecol Oncol. 2002;84:378-82.

66) Enrique E, Marek T, Castello JV, de Mateo JA Usefulness of skin testing with platinum salts to demonstrate lack of cross-reactivity between carboplatin and cisplatin. Ann Allergy Asthma Immunol 2008;100:86.

67) Syrigou E, Makrilia N, Vassias A, Nikolaidis I, Xyla V, Manolopoulos L, Syrigos K. Administration of cisplatin in three patients with carboplatin hypersensitivity: is skin testing useful? Anticancer drugs 2010;21:333-8

68) Gastaminza G de la Borbolla GM, Goikoetxea MJ, Escudero R, Antón J, Espinós J et al. A new rapid desensitization for antineoplastic agents J Investig Allergol Clin Immunol 2011;21:108-12

69) Pagani M, Bavbek S, Dursun AB, Bonadonna P, Caralli M, Cernadas J et al. Role of skin tests in the diagnosis of hypersensitivity reactions to taxanes: results of a multicentre study J Allergy Clin Immunol Pract. 2018;7:990-997

70) Popescu NA, Sheehan MG, Kouides PA, Loughner JE, Condemi JJ, Looney RJ, Leddy JP. Allergic reactions to cyclophosphamide: delayed clinical expression associated with positive immediate skin tests to drug metabolites in five patients. J Allergy Clin Immunol 1996;97:26–33.

71) Weiss RB Hypersensitivity reactions Semin Oncol 1992;19:458-77.

72) Kuo JC, Hawkins CA, Yip D. Application of hypersensitivity skin testing in chemotherapy-induced pneumonitis. Asia Pac Allergy. 2015;5:234-6.

73) Dilley MA Lee JP Broyles A Methotrexate hypersensitivity reactions in pediatrics: Evaluation and management Pediatr Blood Cancer 2017;64:e26306.

74) Galindo-Rodríguez G, Jaime-Pérez JC, Salinas-Carmona MC, Gonzales-Diaz SN, Castro-Corona A, Cavazos-Gonzales R et al. Do immunoglobulin G and immunoglobulin E anti-l-asparaginase antibodies have distinct implications in children with acute lymphoblastic leukemia? A cross-sectional study. Rev Bras Hematol Hemoter. 2017;39:202-209

75) Aberer W, Bircher A, Romano A, Blanca M, Campi P, Fernandez J, et al. Drug provocation testing in the diagnosis of drug hypersensitivity reactions: general considerations. Allergy 2003;58:854–63.

76) Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Ferreiro-Monteagudo R, Guillen-Ponce C, Alvarez-Cuesta E, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assessment. Allergy 2013;68:853–61.

77) Ureña-Tavera A, Zamora-Verduga M, Madrigal-Burgaleta R, Angel-Pereira D, Berges-Gimeno MP, Alvarez-Cuesta E. Hypersensitivity reactions to racemic calcium folinate (leucovorin) during FOLFOX and FOLFIRI chemotherapy administrations. J Allergy Clin Immunol 2015;135:1066–7.

78) Demoly P, Adkinson NF, Brockow K, Castells M, Chiriac AM, Greenberger PA, et al. International Consensus on drug allergy. Allergy 2014;69:420–37.

79) Madrigal-Burgaleta R, Vazquez-Revuelta P, Marti-Garrido J, Lleonart R, Ali FR, Alvarez-Cuesta E. Importance of Diagnostics Prior to Desensitization in New Drug Hypersensitivity: Chemotherapeutics and Biologicals. Curr Treat Options Allergy 2020;7:1-13. DOI 10.1007/s40521-020-00238-y

80) Agache I, Bilò M, Braunstahl G-J, Delgado L, Demoly P, Eigenmann P, et al. In vivo diagnosis of allergic diseases-allergen provocation tests. Allergy 2015;70:355–65.

81) Mayorga C, Celik G, Rouzaire P, Whitaker P, Bonadonna P, Rodrigues-Cernadas J, et al. In vitro tests for drug hypersensitivity reactions: an ENDA/EAACI Drug Allergy Interest Group position paper. Allergy 2016;71:1103–34.

82) Banerji A, Lax T, Guyer A, Hurwitz S, Camargo CA, Long AA. Management of Hypersensitivity Reactions to Carboplatin and Paclitaxel in an Outpatient Oncology Infusion Center: A 5-Year Review. J Allergy Clin Immunol Pract 2014;2:428–33.

83) Hong DI, Madrigal-Burgaleta R, Banerji A, Castells M, Alvarez-Cuesta E. Controversies in Allergy: Chemotherapy Reactions, Desensitize, or Delabel? J Allergy Clin Immunol Pract. 2020; in press. doi: 10.1016/j.jaip.2020.08.005

84) Prieto García A, Pineda de la Losa F. Immunoglobulin E-mediated severe anaphylaxis to paclitaxel. J Investig Allergol Clin Immunol. 2010;20(:170–1.

85) Madrigal-Burgaleta R, Berges-Gimeno MP, Angel-Pereira D, Guillen-Ponce C, Sanz ML, Alvarez-Cuesta E. Desensitizing oxaliplatin-induced fever: a case report. J Investig Allergol Clin Immunol. 2013;23:435–6.

86) Iwamoto T, Sugimoto H, Tabata T, Okuda M. Clinical Utility of Basophil CD203c as a Biomarker for Predicting the Timing of Hypersensitivity Reaction in Carboplatin Rechallenge: Three Case Reports. Clin Ther. 2016 ;38:1537–41.

87) Hesterberg PE, Banerji A, Oren E, Penson RT, Krasner CN, Seiden MV, et al. Risk stratification for desensitization of patients with carboplatin hypersensitivity: Clinical presentation and management. J Allergy Clin Immunol. 2009 ;123:1262–1267.

88) Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. J Allergy Clin Immunol Pract 2016;4:497–504.

89). Brennan PJ, Bouza TR, Hsu FI, Sloane DE, Castells MC. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. J Allergy Clin Immunol 2009;124:1259–1266

90) Breslow RG, Caiado J, Castells MC. Acetylsalicylic acid and montelukast block mast cell mediator–related symptoms during rapid desensitization. Ann Allergy Asthma Immunol 2009;102:155–160.

91) De Angelo DJ Arellano M, Advani A, Damon L et al Prevention and management of asparaginase/ pegasparaginase-associated toxicities in adults and older adolescents: recommendations of an expert panel. Leuk Lymphoma 2011;52:2237-53

92) Polyzos A, Tsavaris N, Kosmos C., Arnaouti T, Kalahanis N, Tsigris C et al. Hypersensitivity reactions to carboplatin administration are common but not always severe. A 10-year experience. Oncology 2001;61:129–33.

93) Brandi G, Pantaleo MA, Galli C, Falcone A, Antonuzzo A, Mordenti P, et al. Hypersensitivity reactions related to oxaliplatin (OHP). Br J Cancer 2003;89:477–81.

94) Lopez-Gonzalez P, Madrigal-Burgaleta R, Carpio-Escalona LV, Bernal-Rubio L, Guerra E, Berges-Gimeno MP et al. Assessment of Antihistamines and Corticosteroids as Premedication in Rapid Drug Desensitization to Paclitaxel: Outcomes in 155 Procedures. J Allergy Clin Immunol Pract. 2018;6:1356-1362.

95) Castells M. Diagnosis and management of anaphylaxis in precision medicine. J Allergy Clin Immunol 2017;140:321-33

96) Sancho-Serra M, Simarro, M., Castells, M. Rapid IgE desensitization is antigen specific and impairs early and late mast cell responses targeting FcεRI internalization. European Journal of Immunology. 2011;41:1004-13.

97) Oka T, Rios EJ, Tsai M, Kalesnikoff J, Galli SJ. Rapid desensitization induces internalization of antigen-specific IgE on mouse mast cells. J Allergy Clin Immunol. 2013;132:922-32

98) 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;126:4103-18.

99) de Las Vecillas Sanchez L, Alenazy LA, Garcia-Neuer M, Castells MC. Drug Hypersensitivity and Desensitizations: Mechanisms and New Approaches. International journal of molecular sciences. 2017;18:1316-1332

100) Sloane D, Govindarajulu U, Harrow-Mortelliti J, Barry W, Hsu FI, Hong D, et al. Safety, Costs, and Efficacy of Rapid Drug Desensitizations to Chemotherapy and Monoclonal Antibodies. J Allergy Clin Immunol: In practice. 2016;4:497-504.