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Hypersensitivity Reactions To Chemotherapy: an EAACI Position Paper

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ABSTRACT

Chemotherapeutic drugs have been widely used in the treatment of cancer disease for about 70 years. The development of new treatments has not hindered their use, and oncologists still prescribe them routinely, alone or in combination with other antineoplastic agents. However, all chemotherapeutic agents can induce hypersensitivity reactions, with different incidences depending on the culprit drug. 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 caused by platinum compounds, taxanes, epipodophyllotoxins and asparaginase. Despite their prevalence and relevance, the ideal pathways for diagnosis, treatment and prevention of these reactions are still unclear, and practice remains considerably heterogeneous with vast differences from center to center. 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. This position paper aims to provide consensus on the investigation of HSRs to chemotherapeutic drugs and give practical recommendations for clinicians that treat these patients, such as oncologists, allergologists and internists. Key sections cover risk factors, pathogenesis, symptoms, the 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, desensitization, drug hypersensitivity, drug provocation test hypersensitivity reactions, **Words Count:** 4896

BOX 1 Definitions and abbreviations

HSRs: Hypersensitivity reactions

CHT: Chemotherapy

DPT: Drug Provocation Test

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ST: Skin tests

SPT: Skin Prick Test

RDD: Rapid Drug Desensitization

RCHU: Ramon y Cajal University Hospital

SCARs: Severe Cutaneous Adverse ReactionsACEI: angiotensin converting enzyme inhibitors

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INTRODUCTION

Chemotherapeutic drugs have been used in the treatment of neoplasms since the 1940s (1,2). Many types of antineoplastic 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). However, CHT can induce hypersensitivity reactions (HSRs) and remains the third leading cause of fatal drug-induced anaphylaxis in the United States (4). Deaths related to CHT have also been reported in Europe (5). This position paper aims to provide consensus on investigating HSRs to chemotherapeutic drugs and give practical recommendations 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, the role of skin tests, in vitro tests, indications and contraindications of drug provocations tests and desensitization of neoplastic patients with allergic reactions to CHT. Table 1 reports the main classes of CHT, their clinical indications, the characteristics of HSRs and their possible pathogenetic mechanisms.

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 analyzed in the position paper. However, the content of this Position Paper was restricted to allergy-like HSRs. The whole group carefully reviewed statements and unmet

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needs, and the quality of evidence and recommendations was discussed and graded by the Task Force members using the SIGN CRITERIA as Grade A, B, C, D. (Table S1) (6, 7).

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EPIDEMIOLOGY AND RISK FACTORS

The correct identification and diagnosis of HSRs to cytostatic drugs plays a crucial role in the treatment of patients with neoplasm because, unlike other drugs (e.g., 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 an HSR occurs, the physician will have to balance the benefits of continuing the treatment versus the risks of a potentially fatal anaphylactic reaction on the next administration of chemotherapy. Hence, the correct diagnosis of an allergic adverse effect to a cytostatic drug is crucial and cannot be postponed. Almost all chemotherapeutic drugs can induce HSRs which 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 (8). 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 (8) (Tab S2). 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 and epipodophyllotoxins, while it is lower with others (9-18). Regarding platinum compounds, carboplatin is the main responsible for HSRs, with an incidence that increases with exposure up to 46% of patients treated with at least seven infusions of the drug (10,11,13,19). Oxaliplatin can induce HSRs in about 15% (range 1-25%) of cases with severe reactions in less than 1%, whereas cisplatin is the culprit drug in about 5% of cases (20). Taxanes can provoke HSRs in about 30% of patients, but the incidence declines to less than 5% with the premedication with steroids and antihistamines (21). The incidence of HSRs to asparaginase ranges from 6 to 43% of cases, increasing after the fourth dose (22,23). The incidence of reactions to epipodophyllotoxins ranges from 6.5% to 41% (17). Most HSRs (> 90%) are not severe.

In studies with different designs 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

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characteristics that have been identified and studied consistently enough to make them a reliable link in managing such HSRs.

1- TAXANES

Risk factors of confirmed HSRs

Drug involved. Taxanes share a highly similar structure (docetaxel and cabazitaxel come from a common paclitaxel precursor), but they may differ in the solubilizer used (e.g., Cremophor EL for paclitaxel, or polysorbate 80 (tween) for docetaxel and cabazitaxel, respectively). Nanoparticle albumin-bound (nab-paclitaxel), devoid of Cremophor EL, seems to have a lower rate of HSRs (24,25), and has been successfully used in several patients with previous anaphylactic reactions attributed to paclitaxel and docetaxel (26,27). However, cross-reactivity between nab-paclitaxel and other taxanes in case of confirmed hypersensitivity (confirmed with skin testing or drug provocation testing) is yet to be adequately studied. Furthermore, there is no data on the use of *in vivo* or *in vitro* techniques to determine this cross-reactivity.

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 (27).

Reaction severity. In the largest study to date on allergy work-up to taxanes (27), patients with immediate moderate to severe HSRs were significantly more likely to have positive skin tests (ST) than patients with a nonimmediate or mild immediate HSRs.

Cross-reactivity: Severe cross-HSRs between paclitaxel and docetaxel were observed in two different studies in a significant proportion of patients with breast and ovarian cancer (28,29).

Risk factors for breakthrough reactions

Patients with negative ST and patients with a nonimmediate or mild immediate index reaction were significantly more likely to resume regular infusion eventually (27).

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2- PLATINUM COMPOUNDS (Carboplatin, Oxaliplatin, Cisplatin)

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 (30-32).

Drug involved. Globally, all chemotherapeutic drugs showed a reduced risk of a confirmed HSR compared to platinum compounds (32).

Previous history of HSR to the same drug. Patients with a history of prior reactions to the same culprit drug showed a 4-fold increased risk of HSR (33-35). In addition, the reaction becomes more severe at re-challenge.

Reaction severity. The initial reaction's severity does not seem to predict a true HSR for some authors (30-32), while for others, change in blood pressure and cardiovascular involvement is a good clinical predictor (33,34). In addition, cutaneous symptoms and gastrointestinal symptoms were independently associated with an increased risk of confirmed HSR (34,35).

CHT schedule. Some studies 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 (35). Furthermore, a number of chemotherapy administrations of six or more represents an important risk factor for the development of HSRs to platinum compounds (36).

BRCA mutations. Patients with BRCA 1-2 mutations show an increased risk of developing HSRs to antineoplastic treatment with carboplatin (37-39).

Risk factors for breakthrough reactions during desensitization: The main predictor for breakthrough reactions is a positive ST result (31,34).

3- ASPARAGINASE

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Native E.coli asparaginase preparation, intravenous administration (40), a prolonged interval between different chemotherapy administrations, and the association with HLA DRB1 07:01 allele are the most important risk factors for developing HSRs (40, 41).

Data about risk factors to epipodophyllotoxins are not available.

Table 2 synthesizes the main risk factors for HSRs to chemotherapy**.**

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PATHOGENESIS

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

TAXANES

Paclitaxel (including 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 (27). 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 (27). One group hypothesized that 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 (42). However, this hypothesis is yet to be confirmed with data.

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 the development of the reaction. (43). Also, specific IgE has been identified in patients who experienced HSRs to platinum agents. (32,44-46) Only anecdotal cases of delayed HSRs that are likely due to T-cell–mediated mechanisms are described after platinum salts administration (47). Therefore, their clinical importance is unclear.

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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 (48). The underlying mechanism is not fully understood. Evidence suggests that HSR to asparaginase may be an IgE-mediated type I reaction, based on the positivity of ST (49). Complement activation mediated by IgG or IgM may also be implicated (50).

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 (17). Both immunologic and non-immunologic mechanisms can be implicated (51). 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

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CLINICAL PRESENTATION

Almost all chemotherapeutic agents have the potential to provoke HSRs. The clinical features and severity of anaphylaxis can be classified according to Brown's classification, in three grades of increasing severity (Table S3). (52)

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 (53). Cutaneous manifestations, such as flushing and/or pruritus, which can progress to urticaria, angioedema, and widespread 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 (54, 55). Other less frequent non-critical symptoms are represented by chills and fever, such as seen with monoclonal antibodies, back and chest pain, probably provoked by nociceptors stimulus mediated by the proinflammatory cascade (56) and hypertension, particularly with taxanes (Table 3).

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SKIN TESTS

In presumed immune-mediated reactions, SPT and intradermal tests performed to detect drug-specific IgE are useful only for a few chemotherapeutic drugs, in particular platinum compounds 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)

As far as taxanes are concerned, positive STs in patients with suspected HSRs to paclitaxel and docetaxel were reported by different authors. These observations demonstrated that at least in some cases, HSRs to taxanes are IgE-mediated (27,59-61). Furthermore, we underline that there aren't experiences regarding STs with emulsifying agents included in the drugs formulations.

Regarding platinum compounds, ST is performed for:

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

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% (62-69). Data regarding ST with cisplatin are limited (63). Carboplatin ST has been investigated as a predictive tool for developing HSRs in patients with recurrent gynaecological 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% (70,71). Regarding oxaliplatin, a study demonstrated a negative predictive value of 95% (30). Therefore, ST for carboplatin and possibly oxaliplatin seem predictive of allergic reaction to these drugs.

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 (72).

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.

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(73,74), but a recent paper demonstrated a very low cross-reactivity between cisplatin and the other platinum salts. (75). Therefore, if it is not possible to utilize another class of chemotherapy, negative ST may be useful in selecting an alternative safe platinum agent.

Regarding other chemotherapeutic drugs, STs tested positive in some patients whith HSRs to other chemotherapeutic drugs such as cyclophosphamide, procarbazine, gemcitabine, metotrexate, and L-asparaginase but the diagnostic and predictive value of these results remains uncertain (76-80).

It's essential to underline that, before administering STs, the allergologist has to wash hands thoroughly with soap and water and wear clean disposable gloves (appropriate for handling chemotherapy), the gown and mask or visor. We would recommend liaison with Occupational Health and Pharmacy.

The best results are obtained when STs are performed in the interval ranging from 6 weeks to 6 months after the allergic reaction (60).

Table 4 shows the non-irritating concentrations of ST for chemotherapeutic drugs

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 SPT is usually negative (Grade C).
- ST for chemotheraputic drugs is also a safety procedure for patients with severe immediate reactions (Grade C).

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- ST concentrations are within a well-standardized range for platinum compounds and taxanes, with local differences amongst groups depending on whether they prioritize sensitivity or specificity (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).
- ST seems predictive of allergic reactions to carboplatin and oxaliplatin (GRADE D)

Unmet needs:

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

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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 (81). DPT is a helpful tool in diagnosing HSRs to CHT 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 (31). However, published data on DPT with CHT are scarce.

In 2013 a pilot experience on the use of DPT for CHT agents was published (82). This experience was further validated in larger studies (31,32), and DPT was found especially useful when more than one drug was involved (83). DPT can also be used to confirm tolerance to cross-reactive alternative drugs, for example, to try different alternatives within the platinum salts family. (75).

Usefulness of DPT

Despite its inherent risks and the lack of universal standardization of optimal protocols for most drugs (84), DPT could prevent non-hypersensitive patients from unnecessary rapid drug desensitization (RDD) procedures when systematically applied before RDD. 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 RDD (31). See table S4.

DPT in practice

According to the vision of EAACI and RCUH (81), the following essential point is paramount for a successful DPT implementation: a "safety first" policy. We cover this at length in the "therapeutical approach" section (see below).

In the RCUH studies, 64% (58/91) (82) and 67% (229/341) (32) of all performed DPTs were negative, and only 4% (4/91) (31) and 5% (17/341) (32) of all performed DPTs showed a severe reaction, according to Brown's classification (52). However low this percentage might be, these reactions are unpredictable, therefore, patient selection must include a careful risk assessment.

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Moreover, the selected location should ideally have 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. (See table 5)

The optimal strategies for introducing systematic DPT in the study of hypersensitivity to CHT are still a matter of discussion and vary locally. (31, 85-88). Recent studies show the experience of one center implementing DPT into their pathways (87,88.

Careful patient selection and locally adapted risk management strategies are of the essence (83,88). DPT is potentially indicated in patients with immediate reactions, anaphylaxis (provided the risk assessment is favorable) and delayed reactions (provided they are non-SCARs) (81). Contraindications for DPT should be the same as the general contraindications for DPT (81), including the lack of access to adequate installations, personnel with expertise in drug allergy, or specific resources that ensure appropriate risk-management plans. Additionally, we should consider the particular 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 (31,32). Table S5 shows an example of DPT or drug challenge with oxaliplatin.

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).

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Unmet Needs:

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

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IN VITRO TESTS

Specific IgE

There is only one case of reported specific IgE for taxanes (59); however, this technique has been widely and successfully used for platins. In addition, early pilot studies showed data on the benefits of implementing specific IgE to study reactions to platins (43,44); See table 6.

In 2015, oxaliplatin-specific IgE was validated in a prospective study in which patients underwent DPT regardless of the sIgE results in the blood samples obtained before the DPT (32) . The authors concluded that both positive ST and oxaliplatin-specific IgE are good tools to confirm oxaliplatin hypersensitivity, but negative results are less useful (32). These conclusions match those of other experiences with ST and sIgE for the study of drug allergy (85).

- Basophil activation testing (BAT) as a diagnostic tool in chemotherapy has only been used in a limited number of cases with platins (89-91).

- 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 (,33,92).

Statements and recommendations:

- In vitro detection of specific IgE for platinum compounds could be a useful tool for the 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

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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 a multidisciplinary institutional collaboration so as to manage these highly complex patients adequately. Specific institutional programs for RDD, led by expert allergists, are 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 (30-34,36,86-89).

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.

Specifically, a recent article featured a practical diagnostic and therapeutic algorithm based on the current knowledge on the topic. (93)

Unmet needs:

- Strengthening the collaboration between specialties
- Universal access to drug desensitization, led by expert allergists

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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 (94). 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% (60), Premedication resulted ineffective in preventing true, IgE-mediated allergic reactions to platinum salts (95). 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 (96). Drugs used in the premedication are able to produce hypersensitivity reactions and should be investigated when a chemotherapy hypersensitivity is suspected.

Statements and recommendations

- Premedication with steroids and antihistamines (e.g., dexametasone 20 mg and chlorpheniramine 10 mg intravenous 1 hour before chemotherapy) is effective for preventing moderate and severe infusion reactions to taxanes, hence that premedication is usually included in local guidelines or the manufacturer's recommendations (GRADE B).
- Premedication with steroids and antihistamines is effective for preventing infusion reactions to epipodophyllotoxins, asparaginase and doxorubicin, hence that premedication is usually included in local guidelines or the manufacturer's recommendations (GRADE D).
- However, premedication is not effective in the case of true IgE-mediated HSRs (GRADE D).

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DESENSITIZATION:

Principles and Practices of Desensitization

RDD is a therapeutic approach delivered through protocols to patients in need of first-line drug therapy (97). It safely administers the needed medication and provides a temporary tolerance to drugs to which patients have presented immediate reactions, including anaphylaxis and selected non-severe delayed reactions. RDD protects from severe HSRs and allows the patients to receive the desired medication within minutes to hours, thereby preventing further delays in treatment for critically ill patients. (98) The principles of IgE RDD are based on *in vitro* and *in vivo* mast cell models. (99-101). Tab 7 reports some of the most significant studies regarding RDD.

Desensitization candidates

Risk stratification is a critical part of RDD qualification and success (Table8).

Low-risk patients usually include those who 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 usually include those who have presented a Grade III HSR and positive ST if 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.

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 an 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 ST is negative and

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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 RDD should be performed and to guide risk stratification.

A DPT may be performed if the test results are negative and the risk assessment is favorable, as explained in the DPT section. If there is no reaction during the DPT, the patient can be sent back to regular infusion. However, if there is a reaction, a tryptase level should be drawn, and RDD should be performed for the subsequent drug exposure.

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

RDD should always be performed in patients with positive ST, 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).

Fig. S1 shows an example of RDD protocol.

Premedication for RDD is usually based on the patient's symptoms during the initial HSR (antihistamines in case of cutaneous symptoms, aspirin and montelukast to prevent bronchospasm, COX-1 inhibitors, steroids and opioids for systemic symptoms including chills, rigors, fever and pain (104). Some authors have used omalizumab in recalcitrant patients, but data are insufficient to recommend this (105). Anyway, despite the premedication, breakthrough reactions occur during and after RDD. The majority of reactions are cutaneous, followed by respiratory and gastrointestinal and occur during the last step of protocol (98). In case of breakthrough reactions, RDD is paused, then the pharmacological treatment depends by the severity of reaction (table 9). There is no going back to previous steps and resolution of 80% of symptoms is sufficient to resume the infusion. If patients experienced reactions require repeat RDD with the same drugs the protocol has to be modified by prolonging the step before when the reactions occurred adding an additional step. Whether reactions persist rate limitations or/and dose reduction should be assessed.

Health care costs and efficacy

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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. (98)

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. (33)

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.ype IV HSR, excluding SCARs are candidates for RDD
- More data on RDD to oral chemotherapeutic drugs

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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.

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Conflict of Interest Statement:

The authors declare no conflict of interest

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Table 1 Main characteristics of the most used CHT agents utilized in clinical practice

Drug category	**Common generic drugs**	**Main Clinical indications**	**Type of HSRs**	**Immunopathogenetic mechanisms of HSRs**
Alkylating agents	Cyclophospamide Ifosfamide Melphalan Busulfan Dacarbazine Thiotepa Carmustine	Leukemia, Lymphomas, Multiple Myeloma, Breast cancer, bladder cancer	Rare, usually mild. Severe cases in very few patients	Not known
Anthracyclines and other antitumor antibiotics	Doxorubicin Epirubicin Bleomycin	Sarcomas, Breast, bladder, lung, thyroid cancer	Rare, namely dermatological effects	Not known
Antimetabolites	5-Fluorouracil Capecitabine Gemcitabine Fludarabine Methotrexate	Gastrointestinal, pancreatic, lung, head and neck cancer, lymphomas, leukemia	Rare, namely dermatological effects	Not Known
Bacterial Enzyme	Asparaginase	Acute Lymphoblastic leukemia	Incidence 6-40%, severe reactions in < 10%	IgE and IgG specific antibodies involved
Cytoskeletal disruptors (taxanes)	Paclitaxel Docetaxel Nab-paclitaxel Cabazitaxel	Breast, ovarian, pancreas, lung, prostate, gastric, head and neck cancer	Usually after the first or second dose. Frequently back or pelvis pain.	Direct mastcell or complement activation. In some cases specific IgE are involved
Epipodophyllotoxins	Etoposide, teniposide	Lung cancer, lymphomas	Up to 40% of patients treated, usually mild	Direct mastcell or complement activation
Platinum-based agents	Carboplatin Cisplatin	Lung, ovarian, gastrointestinal,	Up to 40% for carbo after at	IgE-mediated, especially in most

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	Oxaliplatin	genitourinary cancer	least 7 doses. Severe in < 2%	severe cases. Direct mastcell activation in other cases
Topoisomerase inhibitors	Irinotecan Topotecan	Lung, ovarian, colorectal cancer	Only adenoctal cases	Not known
Vinca Alkaloids	Vincristine Vinblastine	Lymphomas, lung, testicle cancer	Only adenoctal cases	Not known

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Table 2: Risk factors for developing HSRs with CTH drugs

	Taxanes	Platinum compounds	Asparaginase
Presence of atopy	No	No	No
History of HSR to other drugs	yes	yes	No
Age	< 70 years	< 60 years	No
Gender	No	Female	No
Type of cancer	Not known	Not known	Not Known
Most involved drugs	Paclitaxel, Docetaxel	Carboplatin, oxaliplatin	E.coli-asparaginase preparation
Increased severity in previous reactions	Yes	Yes	Yes
Previous history of HSR to individual drugs	No	No	No

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Table 3. 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

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Table 4: Non-irritating concentrations of ST for chemotherapy

Drug	Prick test dilutions (mg/mL)	Intradermal test dilutions (mg/mL)
Paclitaxel	1/10 1 (6)	1/1000 (0,001 [0,006]) 1/100 (0,001 [0,006]) 1/10 (ref. 32)
Docetaxel	1/1 4 (1)	1/100 (0.04 [0.01]) 1/10 0.4 ([0.1])
Carboplatin	1/1 10	1/100 (0,1) 1/10 (1)
Cisplatin	1/1 10	1/100 (0.01) 1/10 (0.1) 1/1 (1)
Oxaliplatin	1/1 5	1/100 (0.05) 1/10 (0.5) 1/1 (5) -some authors have found false positives (ref. 32)-
L-Asparaginase	A drop of reconstitute 5000 KU	0.01 mL of reconstitute 5000 KU
Methotrexate	1/1 10	1/100 (0,1) 1/10 (1) 1/1 (10)
Procarbazine	1/1 5	1/100(0.05)

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Gemcitabine	1/1 38	1/1000 (0.0038) 1/100 (0.038)

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Table-5 Details on drug provocation testing (DPT) with chemotherapy agents as per Ramon y Cajal University Hospital (RCUH) protocol (31,32,92).

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..
Concomitant drugs	**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	

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Restart protocol	is paramount that the patient does not miss or alter their chemotherapy regimes in order to perform a DPT. Therefore, in ase of a positive DPT, once symptoms are controlled after adequate treatment and the patient is asymptomatic, the infusion ay be immediately (approximately within 30 min after the DHR) restarted at 1/4 of the final infusion rate for 15 min,, and en increased to 1/2 of the initial infusion rate until all the medication is administered ('restart protocol'). A phenomenon of mporary 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.

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Tab 6: 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)

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

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Table 7: Results of studies on RDD to CHT

N. of pts	Drugs	N.of RDD	% of cycles completed	Severe HSRs during RDD (%)	Author and Year
17	Taxanes	77	92	0	Feldweg 2005 (102)
98	Platinum compounds, Taxanes, Doxorubicin, Rituximab	413	100	6	Castells 2008 (33)
48	OHP	200	100	0	Wong 2014 (64)
138	Taxanes	940	100	0	Picard 2016 (27)
370	Platinum compounds, Taxanes, Cycloph, Doxorubicin, MoAbs	2177	100	7	Sloane 2016 (98)
515	Platinum compounds, taxanes and other miscellaneous drugs	1027	99	4	Madrgal-Burgaleta 2019 (31)
48	OHP	273	97	4	Silver 2020 (102)
187	Platinum compounds,	648	100	3	Vazquez-Revuelta, 2021 (87) .

Legend OHP: Oxaliplatin; Cycloph: Cyclophosphamide; Moabs: Monoclonal Antibodies

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Table 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, Coronary disease HTA)
No b-blockers No ACEI	B-blockers, ACEI
No pregnancy	Pregnancy

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Table 9: Treatment of breakthrough reactions

Symptoms	Tretament
Pruritus, urticaria	Histamine blockade (AntiH1 and H2)
Bronchospasm	Steroids, oxygen, inhaled beta agonists, montelukast
Flushing	Aspirin
Fever	Paracetamol
Hypotension, syncope	Intravenous cristalloids solutions, steroids and NSAIDs, epinephrine
Criteria of anaphylaxis met	Criteria of anaphylaxis met epinephrine and management of anaphylaxis as per guidelines

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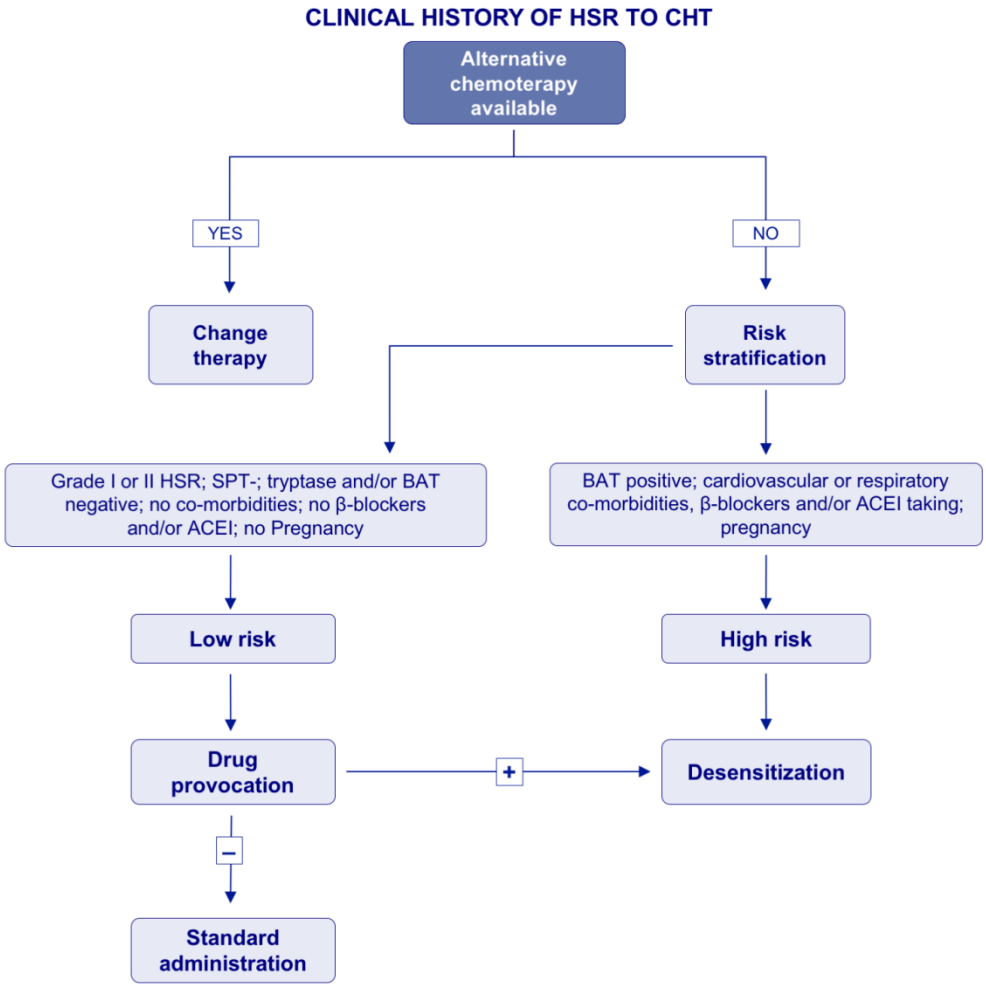


Figure 1_ Pagani et al.

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Name of medication:	*Carboplatin*
Target dose (mg)	250.0
Standard volume per bag (m	80
Calculated final concentration (mg/mL)	1
Standard time of infusion (minute)	187.5

			Total mg per bag
Solution 1	250 mL of	0.010 mg/mL	2.500
Solution 2	250 mL of	0.100 mg/mL	25.000
Solution 3	250 mL of	0.992 mg/mL	248.033

Step	Solution	Rate (mL/hr)	Time (min)	Volume infused per step (mL)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0050	0.0050
2	1	5.0	15	1.25	0.0125	0.0175
3	1	10.0	15	2.50	0.0250	0.0425
4	1	20.0	15	5.00	0.0500	0.0925
5	2	5.0	15	1.25	0.1250	0.2175
6	2	10.0	15	2.50	0.2500	0.4675
7	2	20.0	15	5.00	0.5000	0.9675
8	2	40.0	15	10.00	1.0000	1.9675
9	3	10.0	15	2.50	2.4803	4.4478
10	3	20.0	15	5.00	4.9607	9.4085
11	3	40.0	15	10.00	9.9213	19.3298
12	3	80.0	174.375	232.50	230.6702	250.0000

Total time (minutes)= 339.375 =5.66 hrs

Figure S1_ Pagani et al.

SIGN Guidelines

A: represent At least one meta-analysis, systematic review, or randomized controlled trial (RCT) rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results

B. A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+

C. A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++

D. Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Table S1. Levels of evidence

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1− Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++ High quality systematic reviews of case-control or cohort studies
2+ High quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2− Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3 Non-analytic studies eg., case reports and case series
4 Expert opinion

RCTs, randomized controlled trials.

Table S2: Chemotherapeutic drugs classified on the basis of potential to cause hypersensitivity reactions

Drugs with high potential	Drugs with low potential	Drugs with occasional potential
L-asparaginase (E.coli derived, Erwinia derived, pegasaparaginase)	**Anthracyclines** (daunorubicin, doxorubicin, epirubicin, mitoxantrone, idarubicin, valrubicin)	**Bleomycin**
Platinum-based compounds (carboplatin, cisplatin, oxaliplatin)	**Alkylating agents**	**Topoisomerase inhibitors**
Taxanes (paclitaxel, docetaxel)	**Procarbazine**	**Antimetabolites**
Epipodophyllotoxins (etoposide, tenoposide)		**Vinca alkaloids**

Table. S3: 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. nausea/vomiting 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, (e.g. anxiety or ocular and nasal itching) and there is a significant decrease in blood pressure (systolic <90 mm Hg and/or syncope) and/or oxygen saturation (<92%)

TABLE S4: . Global results on drug provocation testing (DPT) from the largest studies including DPT with different antineoplastic agents.

DPTs	**Patients n = 156** **Ref no:(24)**	**Patients n = 515** **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. (75) 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 S5: 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 8.

Fig S1: Example of 12-step RDD 12 protocol for CHT

Name of medication:	***Carboplatin***
Target Dose (mg)	250.0
Standard volume per bag (ml)	250
Final rate of infusion (ml/hr)	80
Calculated final concentration (mg/ml)	1
Standard time of infusion (minutes)	187.5

					Total mg per bag
Solution 1	250	ml of	0.010	mg/ml	2.500
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*** PLEASE NOTE *** The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are *not completely infused*

Step	Solution	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
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3	1	10.0	15	2.50	0.0250	0.0425
4	1	20.0	15	5.00	0.0500	0.0925
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		Total time (minutes) =	339.375	= 5.66 hrs		

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Table S5: 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

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Fig S1: Example of 12-step RDD 12 protocol for CHT

Name of medication:	***Carboplatin***
Target Dose (mg)	250.0
Standard volume per bag (ml)	250
Final rate of infusion (ml/hr)	80
Calculated final concentration (mg/ml)	1
Standard time of infusion (minutes)	187.5

					Total mg per bag
Solution 1	250	ml of	0.010	mg/ml	2.500
Solution 2	250	ml of	0.100	mg/ml	25.000
Solution 3	250	ml of	0.992	mg/ml	248.033

*** PLEASE NOTE *** The total volume and dose dispensed are more than the final dose given to patient because many of the solutions are *not completely infused*

Step	Solution	Rate (ml/hr)	Time (min)	Volume infused per step (ml)	Dose administered with this step (mg)	Cumulative dose (mg)
1	1	2.0	15	0.50	0.0050	0.0050
2	1	5.0	15	1.25	0.0125	0.0175
3	1	10.0	15	2.50	0.0250	0.0425
4	1	20.0	15	5.00	0.0500	0.0925
5	2	5.0	15	1.25	0.1250	0.2175
6	2	10.0	15	2.50	0.2500	0.4675
7	2	20.0	15	5.00	0.5000	0.9675
8	2	40.0	15	10.00	1.0000	1.9675
9	3	10.0	15	2.50	2.4803	4.4478
10	3	20.0	15	5.00	4.9607	9.4085
11	3	40.0	15	10.00	9.9213	19.3298
12	3	80.0	174.375	232.50	230.6702	250.0000

		Total time (minutes) =	339.375	= 5.66 hrs		