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Drug Allergy (MJ Torres Jaén, Section Editor)

Options in Hypersensitivity Reactions to Chemotherapeutics

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Opinion statement

Purpose of review Chemotherapeutic drugs still represent a gold standard for the treatment of neoplastic disease. They can induce hypersensitivity reactions and are the third leading cause of fatal drug-induced anaphylaxis in the USA. This article has tried to highlight and summarize the most recent scientific progress concerning risk factors, pathogenesis, diagnosis, and treatment of these reactions.
Recent findings Identification of patients at high risk of developing hypersensitivity reactions allows risk stratification to guide clinical decision-making. Therefore, the most recent researches evaluated the possibility to perform risk stratification in case of hypersensitivity reactions to platinum compounds and taxanes. In addition, new data are now available regarding the role of in vitro test for the diagnosis of reactions to platins and the role of drug provocation test in case of hypersensitivity to a number of chemotherapeutics. However, actually, the allergological work-up includes a very careful anamnesis of the patient and the characteristics of reaction, whereas skin tests are useful only for few classes of chemotherapy, namely platinum salts and probably taxanes. Premedication, desensitization and, in some cases, skin tests are able to prevent the majority of hypersensitivity reactions, permitting the administration of the most effective therapy.
Summary Clearly, more studies are needed to better understand, diagnose, treat, and prevent these reactions. To reach this aim, a multidisciplinar approach to the cancer patient with potential allergies is needed.

Introduction

Chemotherapeutic drugs are utilized for the treatment of neoplastic diseases from 1940s, when Gilman and Philips observed that chemical agents utilized during the second World War, named nitrogen mustards, had antineoplastic

activity, inducing dramatic regression of some types of lymphomas [1]. Since then, many types of antineoplastic agents were introduced in clinical practice and, despite the huge diffusion of biological agents, chemotherapy still represents a gold standard for the treatment of the majority of cancers, alone or better in combination with the so called, more selective, targeted therapies such as monoclonal antibodies or other biologicals.

Cancer disease caused 8.8 million of deaths in 2015 and is expected to have an increase by 70% of new cases in the next 25 years [2]. Actually, the research of new treatments is very active worldwide and antineoplastic agents currently available are more than 100. As regards chemotherapeutic drugs, on the basis of their chemical structure and the mechanism they use to attack cancer cells, they can be divided in the following classes [3]

- alkylant drugs (e.g., platinum salts, nitrogen mustards)
- antimetabolites (e.g., folic acid analogues)
- antitumor antibiotics (e.g., anthracyclines)
- plant alkaloids (e.g., taxanes)

The most common adverse effects of non-targeted drugs are related to their activity against proliferating cells such as blood cells, hair follicles, gastrointestinal mucosa, taste buds, and sexual organ cells. Therefore, all chemotherapeutic drugs are capable of causing nausea and or vomiting, myelosuppression with leukopenia, anemia, thrombocytopenia, alopecia, mucositis, and diarrhea [4]. In addition, antineoplastics can induce hypersensitivity reactions (HSRs) and are the third leading cause of fatal drug-induced anaphylaxis in the USA [5]; also in Europe, deaths related to chemotherapy were reported [6].

This review analyses the most recent data about classification, patho-mechanisms, symptoms, diagnosis, and prevention's procedures regarding hypersensitivity reactions to chemotherapy.

Epidemiology, classification, and risk factors

Almost all chemotherapeutic drugs can induce HSRs reported in about 5% of patients even if this percentage is probably underestimated because oncologists often do not signal mild–moderate reactions but only severe ones [7]. 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]. 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, and procarbazine, while it is lower with others. The National Cancer Institute has graded the severity of the reactions in five levels (Table 1) [9].

In recent years, several authors have been trying to identify risk factors for the development of hypersensitivity reactions to chemotherapy, with the aim of reducing or preventing these reactions in subjects most exposed to such adverse effects.

The most investigated drugs were platinum salts, asparaginase, and taxanes and, despite the analysis of several potential risk factors such as sex, history of familiar, or personal allergy, dosage of chemotherapy, only a few risk factors were clearly identified, such as a number of chemotherapeutic dose of eight or more, an interval between cycles longer than 12 months [10–13] or intravenous administration of asparaginase [14]. However, some recent studies have shown that younger age is associated with severe hypersensitivity reactions to taxanes and platinum salts [15, 16]. Finally, a study of breast cancer patients has evidenced that a gene mutation is a risk factor for hypersensitivity reactions to carboplatin [17].

Table 1. Grading of hypersensitivity reactions according to National Cancer Institute's Criteria

Grade	Hypersensitivity reaction
1	Transient flushing or rash Drug fever 38° C (100.4° F) Intervention not indicated
2	Rash, flushing, urticaria, and dyspnea Drug fever 38° C (100.4° F) Intervention or infusion interruption indicated, responds promptly to symptomatic treatment (e.g., antihistamines, nonsteroidal anti-inflammatory drugs, narcotics), prophylactic medications indicated < 24 h
3	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion), recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
4	Life-threatening consequences; urgent intervention indicated
5	Death

Patho-mechanisms

Antineoplastic drugs are able to induce HSRs through the parent compound, their metabolites or the solvent in which they are solubilized. The patho-mechanisms of the hypersensitivity reactions, however, are not intensively analyzed. Similar to other drug reactions, and observing the positive results of skin tests and the detection of specific IgE during in vitro analyses, the most severe acute reactions probably involve drug-specific IgE antibodies, as occurs with the platinum compounds [18, 19•, 20]. The majority of mild–moderate reactions are provoked by other mechanisms such as direct mast cell or basophil activation/degranulation or activation of the complement cascade [21]. In addition, cases of types II, III, or IV reactions have been reported [22–24].

Clinical presentation

The clinical manifestations are variable and unpredictable. In classical cases, symptoms and signs involve the skin, causing erythematous, itchy rash, urticarial/angioedema, palmar erythema, facial flushing, respiratory tract (e.g., cough, rhinitis, bronchospasm), gastrointestinal tract (e.g., abdominal pain, nausea, diarrhea), and cardiocirculatory system (e.g., hypotension and tachycardia). More severe reactions provoke chest pain, angina pectoris, evolving to anaphylaxis, and even, in rare cases, death [25]. Severe reactions characteristically appear during the infusion of the chemotherapy, whereas mild to moderate reactions can occur either during the treatment or during the 24- to 72-h period after the end of the chemotherapy administration [26•].

Diagnosis

The correct diagnosis of an allergic side effect to a cytostatic drug is crucial and cannot be postponed, because unlike other drugs (e.g., antibiotics) that may be easily replaced and exchanged in case of adverse reactions, chemotherapeutic drugs are often uniquely complementary for a particular cancer and therefore, necessary and irreplaceable for the treatment of the disease. Therefore, if a hypersensitivity reaction occurs, the physician may have to decide between the benefit of continuing the treatment and the risk of, for example, a potential fatal anaphylactic reaction during the subsequent chemotherapy. In these cases, a proper patient management makes a multidisciplinary approach between oncologists and allergists indispensable.

The diagnosis of hypersensitivity reactions to a drug is based on history, clinical manifestations, and if possible, skin tests, in vitro tests and provocation tests [27]. In neoplastic patients, anamnestic evaluation is complicated by many confounding factors: (1) the patients often takes a lot of drugs, for example analgesics or anti-emetics that may also provoke hypersensitivity reactions; (2) cancer itself may cause, probably via the direct activation of basophils and mast cells, some clinical symptoms typical of hypersensitivity reactions; furthermore, some epidemiological studies have demonstrated that certain cancers are associated with an increased risk of allergies [28]. In addition, chemotherapy often provokes non immune-mediated hypersensitivity reactions, so in vivo or in vitro tests often are not useful. Therefore, the physician must obtain a careful clinical history, analyzing the characteristics and chronology of symptoms and their relationship to the intake of cytotoxic or other drugs. For example, hypersensitivity reactions to taxanes usually develop during the first or second infusion, whereas reactions to platinum salts occur after several doses of therapy, on average six/seven, suggesting that sensitization to the drug is needed.

In the presumed immune-mediated reactions, prick and intradermal tests performed to detect drug-specific IgE are useful only for few chemotherapeutic drugs, in particular, platinum salts and probably for taxanes. The role of skin test and in vitro test in case of suspected hypersensitivity reactions to platinum compounds and taxanes will be discussed in another section of this paper.

As regards the other chemotherapeutic drugs, skin tests proved positive in patients who reacted to cyclophosphamide [29], procarbazine [30], gemcitabine [31], metotrexate [32], and L-asparaginase [33] but the diagnostic and predictive value of these results remains uncertain. In vitro tests are under investigation and will be treated in the section regarding platinum compounds.

As regards drug provocation tests, interestingly Alvarez-Cuesta et al. recently reported that this diagnostic procedure was negative in 64% of 104 neoplastic patients with suspected hypersensitivity reactions to chemotherapy or biologicals. The authors concluded that implementation of DPT in diagnostic protocols helps exclude hypersensitivity and avoids unnecessary desensitizations in non-hypersensitive patients [34••]. Table 2 summarizes concentrations of chemotherapeutic drugs used for skin testing.

Table 2. Non-irritating concentrations for chemotherapeutic drugs skin testing

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

Preventive measures to avoid hypersensitivity reactions

Currently, clinicians have three available options to prevent hypersensitivity reactions to chemotherapy: premedication, skin testing and desensitization.

Premedication is said to be effective and has been recommended for the prevention of hypersensitivity reactions to different chemotherapeutics such as epipodophillotoxins and pegasparaginase [35], whereas resulted ineffective in preventing true, IgE-mediated allergic reactions to platinum salts [36, 37]. This procedure, instead, has dramatically decreased the incidence of hypersensitivity reactions to taxanes to 2–4% of cases [30] as described later in this article.

The role of skin tests in between chemotherapy courses to predict a reaction has been analyzed only for platinum salts and will be discussed later.

Desensitization may be considered in patients who experienced severe allergic reactions despite premedication, also when skin tests are negative, namely when the culprit drug is not replaceable because more effective and/or associated with fewer side effects than alternative drugs [38, 39•]. The aim of this procedure is to induce a transient tolerance that can be achieved in a relatively short period (on average 6 h), permitting the safe reintroduction of the drug that provoked the hypersensitivity reactions, and is effective in IgE and non IgE-mediated reactions [40]. Desensitization is a revolutionary approach

for the safe reintroduction of immunogenic drugs. Mast cells and basophils have long been known to be the cellular targets involved in desensitization; however, the inhibitory mechanisms of desensitization are still being elucidated. It has been hypothesized that low antigen doses administered incrementally causes internalization of FcεRI receptors and depletes signal transduction agents such as tyrosine kinases Lyn, Fyn, and Syk and this renders mast cell unresponsive to further antigenic stimulation [41••]. The mechanisms in non-IgE-mediated reactions remain unknown but protocols founded on similar principles have been widely successful.

In the field of chemotherapy, most desensitization protocols involve platinum compounds or taxanes, but theoretically desensitizations to other cytostatic drugs could be attempted and might be successful with this procedure. In the scientific literature, many protocols are described, but the best evaluated ones appear to be a 12-step procedure developed by Castells and colleagues [42] in which the patients receive the established dose for chemotherapy divided into incremental steps. In brief, the drug is prepared in three solutions, the first containing a 100-fold dilution of the final target concentration, the second containing a 10-fold dilution, while the third is obtained by subtracting from the final total dose the cumulative dose presented in the first two solutions. Each solution is administered in four steps at increasing infusion rates. This protocol usually provokes adverse reactions especially during the infusion of the third solution, but a temporary stop of the therapy and the parenteral administration of antihistamines and steroids usually permit the continuation of the therapy until completion. In a recent work, Patil and colleagues [43] identified three different groups of patients with hypersensitivity reactions to carboplatin, namely skin test positives, skin test negatives, and skin tests converters, in which skin test results converted to positive during desensitization after an initial negative result. Skin test positives and converters were more likely to have hypersensitivity reactions during desensitization, while true-negative patients could complete the planned schedule of chemotherapy without desensitization. Desensitization is an effective and safe procedure, but it is also rather complex, involving a team of allergists, anesthetists, and nurses and must be undertaken with caution in patients with severe cardiovascular and respiratory diseases [44, 45]. In addition, this procedure should not be performed in severe non-immediate clinical cases such as the Stevens-Johnson syndrome or toxic epidermal necrolysis. Lastly, but very important, desensitization protocols do not alter the effect of therapy. Table 3 summarizes the different possible management approaches after hypersensitivity reactions to chemotherapeutic drugs.

Generally, grade 1 and 2 reactions allow the continuation of the following doses of chemotherapy without modifications. Grade 3 reactions may require the substitution of the culprit drug. If this is not possible, it is recommended to perform, when there is robust evidence of efficacy, a premedication with steroids and antihistamines and/or reduce the rate of infusion or, in alternative, a desensitization protocol. In the case of grade 4 reactions, the rechallenge should be avoided and the drug should be replaced, unless the treatment is curative; in this case, the application of a desensitization protocol should be evaluated.

Table 3. Handling procedures after severe reactions to chemotherapy

Drug	Management after reactions
Platinum compounds	Desensitization
Taxanes	Increase premedication, slow infusion rate Desensitization
L-asparaginase	Substitution with different preparation premedication with steroids or antihistamines Desensitization
Epipodophyllotoxins	Premedication, slow infusion rate Substitution with different preparation
Procarbazine	Discontinue
Anthracyclines	Slow infusion rate Desensitization
Cyclophosphamide and ifosfamide	Discontinue
Cytarabine	Discontinue
Methotrexate	Premedication with steroids or antihistamines Desensitization
Mercaptopurine, azathioprine	Desensitization

Analysis of drugs most involved in hypersensitivity reactions

Platinum salts

Platinum compounds are a cornerstone for the treatment of a number of cancers including the lung, ovarian, gastrointestinal, head, and neck neoplasms. The drugs utilized in clinical practice are cisplatin, carboplatin, and oxaliplatin. Cisplatin was the first introduced at the end of 60s but for its myelo-, neuro-, and nephro-toxicity another platinum salt, carboplatin, was commercialized 15 years later for its less toxic side effects [46].

The newest generation of platinum compound, oxaliplatin, is utilized by 80s and it is more active respect the progenitors in the treatment of gastrointestinal cancers [47]. Carboplatin is the main responsible of hypersensitivity reactions with an incidence that increases with exposure, up to 46% of patients treated with at least 15 infusions of drug. [48–51]. Oxaliplatin can determine HSRs in about 15% (range 1–25%) of cases with severe reactions in less than 1% [26•], whereas cisplatin is the culprit drug in about 5% of cases [52•].

The most important risk factor is represented by repeated infusions of drug with a peak of incidence during the seventh or eighth administration of carboplatin. This typically occurs in the case of ovarian cancer recurrence, during which carboplatin is administered again several months after the last infusion [11–13]. The clinical symptoms are typical of immediate reactions and involves the skin and, in case of more severe reactions, other organ systems with gastrointestinal, cardiac or respiratory symptoms. More rare platinum salts can determine delayed reactions such as cytopenia or macupapular-rash [24, 53, 54].

The diagnostic allergological work-up includes history, in vivo and in vitro tests, and drug provocation test. Skin testing is the main diagnostic tool to detect allergic patients to platinum salts and includes either prick or intradermal tests; in fact, performing prick tests decrease the risk of HSRs during skin tests, whereas intradermal tests need to achieve adequate sensitivity. Patil et al. had demonstrated that the best results are obtained when skin tests are performed in the interval ranging from 6 weeks to 6 months after the allergic reaction [43]. For carboplatin, skin tests are positive up to 100% of patients in the case of severe reactions, whereas the positivity in the cases of oxaliplatin hypersensitivity ranges from 26 to 100% [55]; data regarding skin tests with cisplatin are limited [56].

Carboplatin skin testing has been investigated as a predictive tool for the development of HSRs in patients with recurrent gynecologic cancer who required retreatment with carboplatin. They was shown to have a negative predictive value between 81 and 98.5% and a positive predictive value of 86% [57–59]. About oxaliplatin, in a recent study, 101 patients were submitted to skin testing with this platinum compound. Two patients proved positive, whereas five developed hypersensitivity reactions despite a negative skin test finding (false negative rate 5.05%). These patients underwent desensitization, and the planned schedule of chemotherapy was completed in five cases [60]. Therefore, skin tests for carboplatin and oxaliplatin seem to be useful for the prevention of allergic reaction to these drugs; the tests should be performed on patients after five cycles of chemotherapy containing these drugs, especially when the therapy is re-administered to a neoplastic patient after an interval between the last and the new infusion of more than 12 months. As with carboplatin skin testing, oxaliplatin skin testing is useful for risk stratification of patients who have experienced oxaliplatin-induced HSRs. Wong and colleagues have shown that patients with positive skin testing are more likely to experience HSRs during desensitization compared with patients with negative skin testing [61].

In vitro tests are still under development and are not available in clinical practice. Pagani et al. detected specific IgE for carboplatin in three patients positives also to skin tests [62], whereas Madrigal-Burgaleta et al. reported sensitivity of 54 and 38% when using a cut-off of 0.10 and 0.35 UI/l, respectively, and a specificity of 100% of oxaliplatin specific IgE in 13 oxaliplatin-reactive patients [63]. The role of specific IgE was also investigated by Cajado et al. in 24 allergic patients (12 carboplatin and 12 oxaliplatin) and 17 controls. The authors observed a better specificity of oxaliplatin sIgE (75 vs 58.3%), but oxaliplatin sIgE was also detected in 3/12 controls (25%) lowering the specificity. Furthermore, in this report, the authors found a very high cross-reactivity rate, especially when patients were primarily sensitized to oxaliplatin (89% cross-reactivity with the other two platins) and 28.5% between carboplatin and cisplatin. In this cohort, carboplatin-reactive patients did not present with positive oxaliplatin sIgE. Patients sensitized to oxaliplatin appear to have a higher cross-reactivity rate to other platinum agents [64•].

Another very interesting in vitro test is BAT; in fact using CD203 and CD63 as activation markers can identify patients with severe reactions to carboplatin as described by Iwamoto and colleagues and Giavina-Bianchi and colleagues [65, 66].

For the management of patients that developed HSRs to platinum compounds premedication is not useful to avoid severe reactions [36, 37]. Instead,

desensitization is very effective in this kind of patients in delivering the planned dosage of chemotherapy in a monitored setting. The most evaluated protocols are the classical 12-step [42] yet described and the 8-step protocol in which the drug is prepared in two solutions instead of three and administered faster [43]. The choice of protocol is based on the results of skin tests performed before each desensitization. Patients with positive tests undergo the 12-step protocol, those with negative tests undergo the 8-step protocol. In the case of three consecutive negative tests without reactions during desensitization, patients receive the subsequent doses of drug in the outpatient setting [55].

Cross-reactivity to other platinum-containing drugs can occur; so skin tests must be performed also to evaluate this problem for the risk that an allergic patient to a platinum salt is also allergic to an alternative one. In fact, some reports describe severe HSRs to cisplatin and oxaliplatin in patients with previous allergic reactions to carboplatin [67, 68]. Therefore, if it is not possible to utilize another class of chemotherapy, negative skin testing may be useful in selecting an alternative safe platinum agent as demonstrated by Legui-Seguin and confirmed by other smaller studies [56, 69, 70].

Taxanes

Taxanes (paclitaxel with its solvent-free formulation, abraxane and docetaxel) are anticancer drugs that bind to microtubules, stabilize cells, induce cell cycle arrest, and ultimately induce apoptosis [71]. Utilized alone or in combination, they are effective in many neoplastic diseases, namely the ovarian, breast, non-small cell lung, prostate, pancreatic, and gastric cancer. Paclitaxel is a natural molecule isolated from the Pacific yew tree and docetaxel is a semi-synthetic molecule derived from European yew tree needles [72]. Both formulations are solubilized in solvents, respectively Cremophor EL for paclitaxel and polysorbate for docetaxel. The incidence of HSRs were found to be about 30% in the first phase II trials [73, 74], but declined to less than 5% with the widespread of premedication with steroids and antihistamines [75].

The pathomechanism of HSRs is not well defined and until a few years ago, it was thought to be non IgE-mediated with direct mast cell or complement activation provoked by moiety itself or solvents. However, in the last years, positive skin tests in patients with suspected HSRs to paclitaxel and docetaxel were reported by different authors [63, 76] doing speculate that at least in some cases allergic reactions are IgE-mediated. This hypothesis is corroborated by the results of Piccard et al. who observed a 71% of positive results performing skin testing in 143 patients with HSRs to taxanes [77••].

Clinical manifestations usually develop in the first few minutes of the first or second infusion of the drugs and are typical immediate reactions. Differently by platinum salts taxanes can provoke back or pelvis pain and crushing chest [42].

The role of premedication with antihistamines and steroids in the management of HSRs to taxanes is fundamental. To this end, in a recent meta-analysis Chen and colleagues concluded that premedication with oral dexamethasone is more effective and safer than parenteral dexamethasone [78]. Furthermore, recent findings by Berger et al. [79] demonstrated that premedication was not mandatory after two doses of paclitaxel if patients did not develop hypersensitivity reactions. This observation is undoubtedly interesting but more studies

are necessary to confirm the results. Another modality of treatment emerged from the clinical trials of Olson and colleagues [80] and Markman et al. [81]. Both authors re-administered paclitaxel to patients who experienced hypersensitivity reactions to the drug on the same day as the reaction: 93% of the patients were able to complete the planned chemotherapy without reactions. The mechanism postulated by the authors is that the first reactions depleted the mediators responsible for the symptoms.

Interestingly, Piccard et al. re-exposed 164 patients with HSRs to taxanes to the culprit drug administered by desensitization, challenge or both, depending on the severity of the reaction and the result of the skin tests with the aim of resume regular infusion of drug. The authors concluded that this modality of taxanes reintroduction is safe and allows a significant number of patients to resume regular infusion [77••].

Asparaginase

This bacterial enzyme is a cornerstone of treatment for acute lymphoblastic leukemia and has been incorporated into every pediatric protocol as well as many adults protocol of therapy [82]. The sources of L-asparaginase used in clinics are bacterial in origin: an *Escherichia coli* derivative or an *Erwinia chrysanthemi* derivative, it is also available in a polyethylene glycol form, PEG-asparaginase.

The adverse events related to L-asparaginase include nausea, vomiting, myelotoxicity, hepatic failure, and hypersensitivity reactions, this drug being the one with the highest potential to cause these events. The incidence of allergic reactions ranges between 6 and 43%, with serious anaphylactic reactions occurring in fewer than 10% of patients treated. The overall risk of a reaction per drug dose is 5 to 8% with an increase to 33% after the fourth dose [83, 84]. The different incidence depends from a number of factors, including the asparaginase preparation, intensity and consistency of dosing, route of administration, concurrent chemotherapies, and patients genetics. In particular, native *E. coli* asparaginase preparation [85] intravenous administration [23], a prolonged interval between different administrations of chemotherapy [86], and the association with HLA DRB1 07:01 allele are the most important risk factors for the development of HSRs [87•]. L-asparaginase determines the formation of specific IgE and IgG antibodies that decrease the activity of the enzyme and induces the development of allergic reactions [88, 89].

The majority of reactions to asparaginase are mild and often manifest with localized rush or pain around the site of injection, but it is possible to observe severe reactions involving respiratory and cardiovascular system [83]. Usually, HSRs develop in the first hour but, in the case of PEG-asparaginase, they may appear hours after the administration of the drug [90]. The role of skin test as a diagnostic tool in uncertain but recently Galindo Rodriguez et al. observed positive prick tests in 62% of children with HSRs to asparaginase [33].

The management of HSRs to asparaginase includes the switch from *E. coli* derived form to PEG-asparaginase, less immunogenic or, in case of HSRs to both the formulations to *E. chrysanthemi* preparation [87•]. Premedication with steroids is not indicated whereas desensitization have been done successfully for patients reactive to all formulations [91, 92].

Epipodophyllotoxins

These are chemotherapeutic drugs belonging to the topoisomerase II inhibitors class; epipodophyllotoxins utilized in clinical practice are teniposide and etoposide. Teniposide is used for the treatment of hematologic and neurologic malignancies.

Hypersensitivity reactions have long been recognized as one of its toxic effects. The overall incidence of reactions varies from 6.5% observed by O'Dwyer and colleagues, especially in the treatment of brain cancers, to 41% reported by Kellie on 108 children with leukemia [21]. Most of the reactions (> 90%) are of grade 1 or grade 2 severity, even if cases of anaphylaxis occur. The reactions appear after the first dose but more often after many doses, within either the first few minutes of infusion or hours after administration [30]. The pathogenetic mechanism is not well elucidated. Teniposide is dissolved in cremophor EL, which is considered by many as being responsible for the reactions and to this end, recently, He et al. reported that a cremophor-free teniposide was safer as respect the classical formulation [93].

Etoposide was introduced into clinical practice 40 years ago for the treatment of small cell lung cancer, hematological malignancies and refractory testicular cancer and can cause hypersensitivity reactions less commonly than teniposide. It is available for intravenous and oral formulations. The clinical characteristics of reactions are similar to teniposide and are associated only with the intravenous compound, which is dissolved in polysorbate 80 [8]. This fact supports the hypothesis that the solvent may be the culprit of reactions. However, recently, Sambavisan and colleagues have shown that administration of solvent-free etoposide phosphate in subjects with previous hypersensitivity reactions to cremophor formulation is not always safe, but can determine HSRs in some subjects [94].

Premedication with histamine (H1 and H2) blockers and a slow infusion rate may reduce the risk of further hypersensitivity reactions on rechallenge with epipodophyllotoxins [95]. Hudson and colleagues reported a successful rechallenge in 75% of 24 children with hypersensitivity reactions to etoposide. Moreover, they observed three cases of reactions in five children when etoposide was replaced by teniposide [96]. Therefore, the substitution of etoposide with solvent-free formulation or with teniposide is not recommended.

Conclusions

All chemotherapeutic drugs, except nitrosoureas, have caused at least some hypersensitivity reactions that are increasing as cumulative exposure increase. The management of patients with hypersensitivity reactions requires a multidisciplinary approach that includes an integrated assessment of the allergy specialist, oncologist and, in case of comorbidity, of the internist. This approach will best manage high risk patients at various stages represented by the following: (1) treatment of acute reaction, (2) clinical judgment to guide continuation of the same chemotherapy, (3) performing skin tests when indicated, and (4)

desensitization but only by experienced health personnel in this procedure. Risk stratification will be able to guide decision-making for high risk patients.

Compliance with Ethical Standards

Conflict of Interest
Mauro Pagani declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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