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Drug Allergy (C Mayorga, Section Editor)

Importance of Diagnostics Prior to Desensitization in New Drug Hypersensitivity: Chemotherapeutics and Biologicals

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Abstract

Purpose of review In this review article, we intend to summarize the diagnostic tools available for the study of drug hypersensitivity reactions to chemotherapy and biologicals, based on the experience and controversies of the main research groups leading the topic.
Recent findings Recent publications with large cohorts of patients reacting to these drugs are allowing for a better understanding of phenotyping, endotyping, and optimally managing these patients.
Summary There is a remarkable heterogeneity on the diagnostic and therapeutic approach among the different groups, and yet this has allowed for very interesting discoveries. Clinical history alone is insufficient for a diagnosis, but in vitro and in vivo biomarkers are essential for personalized management plans and precision medicine. Drug provocation testing is an essential tool and criterion standard. Despite heterogeneity, dedicated multidisciplinary drug

desensitization program/unit, with dedicated space and personnel for their activities, have shown to be the optimal approach. In this acticle, we provide detailed information on diagnostics tools, with an specific focus on drug provocation testing. Looking forward, collaboration, standardization of techniques, and generalization of solidly established drug allergy teams in large hospitals are fundamental steps for the specialty of allergy in the twenty-first century.

Introduction

In the last years, the availability of a wider range of treatments and the proliferation of precision medicine have clearly changed the frame for patient management in neoplastic and inflammatory diseases. As a result of this, we have experienced an increase in the number of patients who receive different treatments and who do so for longer periods; concurrently, we have observed an increase in the chances of sensitization and, thus, the onset of drug hypersensitivity reactions (DHRs) [1••, 2•, 3].

The formal diagnosis and personalized management of DHRs is based on clinical history, skin testing, in vitro testing, and drug provocation testing [4, 5]. A proper diagnosis is key for a tailored therapeutic plan, which basically aims for de-labeling, avoidance, or desensitization if needed/possible. This approach was recently summed up in a phrase by Castells [6]: "veni, vidi, vici-come, understand, and delabel, avoid, or desensitize". The author suggests to, first, come and spend time learning about the reaction to observe the signs and symptoms. These data can used to observe the phenotype, to understand the endotype, and to get help from the biomarkers (tryptase, skin testing, in vitro testing, drug provocation testing, genotype) and, finally, to provide an appropriate treatment option, to recommend avoidance or desensitization if possible and/or indicated, and to de-label all nonallergic patients.

An accurate diagnosis is essential, as both underdiagnosis and over-diagnosis are potential problems [4, 7]; likewise, expanding on this, access to drug allergy specialist centers (with trained staff and adequate installations) is *de rigueur*. Mislabeling of drug allergy and difficult access to trained allergists can truly impact individual treatment plans, can be a financial burden for health providers and, alarmingly, can cause harm to patients by forced changes to alternative treatments that might be less effective (thus, impairing the prognosis and/or quality of life) or might come with significant side effects [1••, 2•, 4, 7].

Despite the efforts of active groups that endeavour to provide us with standardized operating procedures (such as the European Network of Drug Allergy, the USA Practice Parameters, the British Society for Allergy & Clinical Immunology, or the Spanish Society of Allergology and Clinical Immunology), the validation of clinical tests is still difficult, as there is a remarkable lack of multicenter studies and the heterogeneity in practices most times renders data comparison impossible [4, 8–16].

Unfortunately, heterogeneity is a very present reality for new drug hypersensitivity, which includes not only drugs that are genuinely of a recent release (such as many biologicals) but also drugs that might have been in the market for a long time and yet are relatively new for the allergist (such as chemotherapeutics). Regretfully, quite often, both the complexities of these drugs and the lack of resources discourage many from properly dealing with the study and management of these reactions, and this forces other non-allergist specialists (without the specific knowledge, or training, or access to adequate installations) to manage these patients in a suboptimal way. That being said, many allergy departments have successfully taken the initiative of starting up drug desensitization programs/units, which are certainly inspiring examples for the specialty of allergy in the twenty-first century, and actively provide us with further insight and innovations on the topic [1••, 2•, 17••, 18–22, 23••, 24–32, 33•, 34–36, 37•]. We will try to effectively summarize all the key relevant learnings in this manuscript.

Criterion standard for drug allergy diagnosis

The final criterion standard to reach a diagnosis is the drug provocation test (DPT), and all other diagnostic tools can be considered risk markers to aid us with the

decision-making process on whether the patient could be a candidate for DPT [17••, 38–41]. These diagnostic risk markers are useful tools, because they can not only provide us with information on the likelihood ratios for a positive or a negative DPT (and, thus, a final diagnosis) but also provide us with invaluable information on phenotypes and endotypes [1••, 5, 33•, 38, 39].

In vitro diagnostic risk markers

Drug allergy in the twenty-first century is evolving toward a new Precision Medicine approach, which allows for a personalized management based on phenotyping/endotyping and genotyping. However modest, some progress has been made in identifying biomarkers for the fundamental endotypes in the field of hypersensitivity to chemotherapy [5].

In vitro techniques for the study of drug allergy still suffer from low grades of recommendation, because not many tests are licenced, many are offered with no validation whatsoever, or rather base their validation on data from small studies with few subjects that are often diagnosed by clinical history alone [8, 39].

In this section, we will cover in vitro techniques for evaluating hypersensitivity to chemotherapy which rely on published data, namely, total IgE, specific IgE, basophil activation test, and mediator release (tryptase).

Total IgE

Total IgE has been found to be a good predictor of a final positive diagnosis of allergy in platin-reactive patients, with an RRR of 1.46 (95% confidence interval, 1.00–2.40) [1••]; however, more studies in different populations are needed to further explore this.

Specific IgE

There is only one case report of a positive taxane-specific IgE [42]; otherwise, virtually all published data on chemotherapy-specific IgE are clutched by platins. Pagani and colleagues [43] were pioneers when they reported initial data on carboplatin and cisplatin-specific IgE on carboplatin-reactive patients in 2012.

In 2013, a prospective study with 23 oxaliplatin-reactive well-characterized patients (diagnosed after a protocol including systematic skin tests (STs) and DPT regardless of the specific IgE results) reported how oxaliplatin-specific IgE could be very specific but less sensitive, but the authors suggested that larger studies were needed to validate the technique [20].

That same year, a study with 12 carboplatin-reactive patients and 12 oxaliplatin-reactive patients, found that carboplatin-specific IgE probably had a higher specificity and a lower sensitivity when compared with oxaliplatin-specific IgE [44]. In this study, two oxaliplatin-reactive patients were diagnosed as cases based on clinical history, and the remaining 10 patients had positive ST. This article was a retrospective case study with a small sample size, and the authors stated that their preliminary conclusions could not be extrapolated, and yet they reported interesting cross-reactivity data between platins detected by specific IgE (with oxaliplatin appearing to be the most immunogenic platin).

These pilot studies showed clear data on the benefits of implementing specific IgE, because (once validated) this technique could identify allergic patients that ST might miss and thus prevent them from DPT. For example, one oxaliplatin-reactive patient had a negative ST and a positive DPT, and his oxaliplatin-specific IgE was 1.44 UI/L [20]. On the other hand, they brought to the forefront important unresolved issues, such as false positives, adequate cutoff points, and adequate criterion standards for validation. For example, in the study by Caidao [44], there was a control group of 12 patients who had been exposed to oxaliplatin. They found two patients with positive intradermal tests and specific IgE results of 0.14 and 0.16 IU/L (which were considered positive on that study). Most interestingly, these two patients tolerated further regular oxaliplatin infusions uneventfully. The authors were unable to explain these false positives.

A study published in 2015 could validate oxaliplatin-specific IgE in a prospective study including a cohort of 74 oxaliplatin-reactive well-characterized patients (diagnosed after a protocol with systematic DPT as criterion standard regardless of the specific IgE results) [17••]. This design allowed for calculations of predictive values and likelihood ratios, being the latter more interesting in a precision medicine setting. The authors concluded that, whenever positive, both ST and oxaliplatin-specific IgE are good tools to confirm oxaliplatin hypersensitivity, however, negative results are less useful and require of DPT to reach a diagnosis. Unsurprisingly, these are the conclusions that we often find whenever using ST and specific IgE for the study of DHRs [8]. This study implies that no technique alone, but the combination of techniques and their likelihood ratios could be more useful for endotyping, and optimally assessing

risks. The authors also made relevant observations on patients with long elapsed times from the initial reaction to the DPT (who might present with a false-negative DPT), and how follow-up with specific IgE in such patients might be useful to identify positive converters.

Similar to what has been found for ST [34], the usefulness of these techniques could be different depending on the population to which we apply them. Therefore, more studies are necessary to answer these questions in different populations and for other chemotherapy drugs.

In conclusion, specific IgE is a useful biomarker (in combination with ST) for (i) identifying an IgE-mediated endotype, (ii) studying cross-reactivity, (iii) as a risk marker prior to DPT or rapid drug desensitization, (iv) and could be useful in follow-up of negative drug provocation testing in patients with a long elapsed time from initial reaction to DPT.

Basophil activation test

The use of basophil activation test (BAT) as a diagnostic tool in chemotherapy was first reported in one isolated case of an oxaliplatin-reactive patient [45], and in a prospective study with a small series of carboplatin-reactive cases by Iwamoto and colleagues [46]. Additionally, this group explored the possibility of using BAT as a predictor tool with promising results [46, 47]. Recently, another group has explored the use of this tool in a series of 15 patients reacting to platinum compounds, with promising results even as a tool to predict severity [48•]. Nevertheless, the authors of these articles acknowledge difficulties using BAT in clinical practice [47], and the need for standardization/validation [45]. Thus, the use of BAT is still limited to research or as a complementary tool for selected patients in expert centers.

Mediators

Tryptase determination during the acute phase is a useful biomarker for confirming mast cell mediated reactions [8]. When compared with a baseline determination, it is useful during the study of the initial reaction, during positive DPTs or even reactive rapid drug desensitizations (RDDs) for better endotyping of the reaction and tailored planning for future procedures [17••, 32, 49]. Serum baseline tryptase has also been used as a risk biomarker for identifying chemotherapy-reactive patients with systemic mastocytosis [21].

Peripheral blood tests may be useful for endotyping when type II hypersensitivity is suspected (such as immune thrombocytopenia and hemolytic anemia) or to discard infection when atypical symptoms like fever appear [45, 49]. These samples may also be used to study inflammatory biomarkers (e.g., IL-6, TNF-α, IL-1β) [8, 49].

In vivo diagnostic risk markers (skin testing)

ST is the most widely used method to identify allergic sensitization, and yet we are surprisingly lacking international consensus on standard operating procedures, optimal drug concentrations, and interpretation [50]. This is especially true for antineoplastic and biological agents, as even the main research groups describe unalike methodologies, approaches to the technique, and even concentrations [1••, 17••, 24, 26, 34, 50].

ST needs to be used according to the suspected pathomechanism of the DHR [51, 52]. Most reactions with antineoplastics and biologicals are immediate reactions in which we need to study a possible IgE-dependant mechanism, most of the data on ST with these new drugs are on immediate reading skin prick testing (SPT) and intradermal testing (IDT) [1••, 17••, 24, 26, 34]. On the other hand, nonimmediate reactions with a suspected T cell-mediated mechanism will benefit from patch testing, photopatch testing, and/or delayed reading of IDT [51–53].

Methodology

The European Academy of Allergy and Clinical Immunology (EAACI) [52] recommends that SPT should be performed by pricking the skin percutaneously with a prick needle through an allergen solution, followed (if negative SPT) by IDT, which is performed injecting 0.02 to 0.05 ml of an allergen intradermally, raising a small bleb measuring 3 mm in diameter. Both techniques should be performed on the volar aspect of the forearm and read within 15 to 20 min. Reactions are considered positive when the size of the initial wheal increases by 3 mm or greater in diameter after 15 to 20 min and is associated with a flare.

Interpretation of STs is no easy task, and this is true for SPT and even more so for IDT (as we risk false-positive results) [17••, 52]. According to EAACI [52], "the mean diameter is recorded by measuring the largest and the smallest diameters at right angles to each other. Both diameters are recorded, summed and divided by 2". Interestingly enough, the

American Academy of Allergy, Asthma & Immunology (AAAAI) uses slightly different criteria by adding comparison with the negative control: "a prick/puncture test with a response of at least 3-mm diameter (with equivalent erythema) more than diluent control done at the same time is required as proof of the presence of cutaneous allergen specific IgE", and they discuss different possibilities for interpretation of STs [54]. Additionally, some authors in Nordic countries, use the wheal and flare of a positive control histamine test to assign biologic equivalency to allergen materials, bioequivalency by this system is defined as histamine equivalent prick (HEP) units and used for comparison reference standard. Their data show that this method can reduce the influence of differences in test technique among assistants and centers, and so responses to allergen-induced skin prick tests should be compared with that of histamine [55]. The Ramon y Cajal University Hospital (RCUH) uses EAACI recommendations [1••, 52]. The Brigham and Women's Hospital (BWH) uses the AAAAI recommendations [54, 56]. Massachusetts General states [26]: "a positive ST result is defined as either a wheal that is at least 5 mm in largest diameter with a surrounding flare or a wheal with a largest diameter 3 to 5 mm longer than that of the negative control".

Different groups might use different methodology depending on whether they want to focus on better specificity or sensitivity, however, the methodology used for STs should be very clearly stated on research articles. Without common methodology, data on STs from different groups are rendered almost useless for face to face comparison.

There are yet unknown reasons for remarkable differences in sensitization patterns in different populations, and this is particularly noticeable for example in the surprising numbers of patients with positive STs to taxanes limited to the BWH population [34], or the low sensitivity for oxaliplatin ST and specific IgE in the RCUH population [1••, 17••].

Concentrations

Most groups use similar non-irritant concentrations, and yet there are minor differences depending on individual observations mostly on the higher dose for IDT [1••, 17••, 24, 26, 34, 50]. For example, the BWH uses carboplatin for IDT at 10 mg/ml [23••], whereas Massachusetts General considers that this concentration might be more sensitive, but is prone to necrosis [26–29, 57••], and the RCUH considers there is the risk of false positives (after finding patients with positive STs at that concentration who had a negative DPT) [17••]. The RCUH also found the higher IDT doses for paclitaxel (6 mg/ml) and oxaliplatin (5 mg/ml) to cause false positives, and so that group has then used 1/10 of those concentrations for IDT, and so do other groups [37•], and so is proposed in the official EAACI recommendations [50]. Four large centers propose oxaliplatin at 5 and 0.5 mg/ml as the top concentrations for oxaliplatin [1••, 2•, 17••, 23••, 28, 37•]; on the other hand, interestingly, the EAACI proposes 1 and 0.1 mg/ml for oxaliplatin, based on one study [58]. As discussed above in the in vitro diagnostic risk markers section, the BWH found at least two clear cases of false positives IDT to oxaliplatin at both 5 and 0.5 mg/ml concentrations [44].

An article published in 2009 by the BWH [59] showed how doses for monoclonal antibodies were empirically obtained, and those concentrations were also found non-irritant by other groups [1••, 20]; in short, full-strength solution according to manufacturer's instructions (maximal concentration) and diluted further in normal saline to 1/10 (minimal concentration).

It is fair to say that, even if every group makes use of their own set of non-irritant concentrations, no multicentric studies have been designed to compare the diagnostic value of different concentrations and finally decide on the ideal concentrations. And this is clearly an area that needs more systematic investigation.

Safety

Performing ST with antineoplastics and biologicals requires careful planning before implementation, as it is resource intensive and allergy practices need to adapt to the requirements of the drugs. The dilutions need to be prepared by pharmacy specialists, staff must be trained in the handling of these drugs (protection, disposal, occupational health controls, etc.), and the dedicated space for skin testing with these agents must comply with local regulations on hazardous drugs handling [1••, 24].

Systemic allergic reactions have been reported, essentially with IDT, and thus ST must be performed in an area that is prepared for the management of anaphylaxis [1••, 17••, 26, 52, 60]. But other kind of reactions, such as irritation and necrosis, are possible, and thus staff performing these techniques need to be specifically trained [1••, 17••, 57••].

Timing

The EAACI recommendations state [52] that there is a consensus of opinion that STs should be performed after a time interval which allows resolution of clinical symptoms, clearance from the circulation of the incriminated drugs and anti-allergic medications, and that many groups carry out tests after some minimal time interval of, for example, 3 weeks, but not more than 3 months, if possible, as sensitization could decrease over time. Experience on hymenoptera venom [61] show that during the first 4 to 6 weeks following a systemic reaction there is a higher risk of false-negative results on ST; and clinical experience on the study of chemotherapeutics shows similar data [57••]. Different groups have found that longer periods from the initial reaction (> 6 months) are also associated with false-negative results [17••, 57••].

Application of ST-based risk stratification pathways

The Massachusetts General group has dedicated most of their research focus on the devising of ST-based risk stratification pathways that beautifully deal with most of the issues linked to ST timing-related problems (especially false negatives) and that aim to progressively transition patients that might not be allergic into standard infusions [24–26, 28–30]. The more direct approach of the RCUH, using DPT on the front line, deals with platin ST false negatives with follow-up of negative DPTs with ST in order to identify "positive converters" [1••, 17••]. The RCUH officially includes the possibility of false positives on the study pathways and considers DPT as an option for such cases [1••, 17••].

Drug provocation testing

Data on the use of DPT for the study of DHRs to antineoplastics and biological agents are scarce. The first reported data of systematic DPT with antineoplastics and biologicals with a clear positioning on its vital importance were published by the RCUH [17••]. Later on, other groups included the possibility of using this procedure (labeled as "challenge" or "rechallenge") in the diagnostic charts of several articles for some patients [29, 34]. However, the largest reported series (with over 300 procedures) of systematic DPTs with these drugs have been reported by the RCUH [1••, 17••].

Indications

(1) To exclude hypersensitivity and avoid unnecessary desensitizations, either to drugs which have been involved in a DHR or to drugs with a reported cross-reactivity.

DPT has been used for studying DHRs to many drugs and the general learning is that an "unequivocal" clinical history is not enough to reach a diagnosis, because around 20 to 80% of those patients will show a negative DPT [17••, 38, 63–69]. "Misclassification based on the DHR history alone may limit therapeutic options and can lead to the use of more-expensive and potentially less-effective drugs" [4, 40].

Some authors have discussed how identifying non-hypersensitive patients who may receive standard infusions (i.e., with no need for desensitization) leads to fewer unnecessary desensitizations and improved patient care [28]. In the RCUH study on DPT with chemotherapy and biological agents [17], from 30 to 56% of 186 patients who had been referred after suffering a DHR with these drugs, showed a negative DPT and therefore could avoid desensitization.

(2) More than one drug is involved in the initial reaction. The clinical picture of DHRs with chemotherapeutic and biological agents becomes especially complex when more than one drug is involved in the DHR (other antineoplastics, adjuvant drugs, antiemetics, etc.), and (as it usually happens) most of them are unique and essential for the treatment of the patient, and the correct diagnosis cannot be postponed [70].

Some drugs are even administered simultaneously, as for example oxaliplatin and leucovorin. When a drug like leucovorin is administered along a "more likely" culprit drug for DHRs (e.g., oxaliplatin), the former drug (leucovorin) may be overlooked as a responsible agent. Leucovorin was found to be the real culprit drug in up to 11% of oxaliplatin-reactive patients, and implementing systematic DPT prevents a considerable amount of patients from being falsely diagnosed as hypersensitive to oxaliplatin and/or avoids falsely "unsuccessful" desensitizations (undiagnosed leucovorin-hypersensitive patients who are desensitized to oxaliplatin but persistently react when leucovorin is administered) [19–22, 23••,

24–32, 33•, 34–36, 37•, 38–47,48•, 49, 50–56, 57••, 58–61, 62•, 63–71].

(3) Diagnostic tools validation and other scientific purposes. Diagnostic tools should be validated according to an optimal criterion standard, which is DPT [17••]. Additionally, DPT may help understand the mechanisms and phenotypes of DHRs. All this information will be extremely useful for patients. However, only expert Drug Allergy centers with specific objectives and specific approval by institutional ethic boards should include this indication [38]. On this note, DPT with antineoplastic and biological agents has been helpful for identifying false-positive concentrations for STs, identifying predictors of a hypersensitivity diagnosis, or proposing different patient phenotypes [17••].

Patient selection and location

Selecting the adequate patient for DPT is an important step to ensure safety. In the RCUH study [17••], 64% (67/104) of all performed DPTs were negative, and only 4% (4/104) of the patients showed severe reaction. However, we need to make sure a priori that all candidate patients could withstand a possible severe reaction. The selected location in that study was the Medical Intensive Care Unit [17••], given that no previous experience had been reported, given that potentially severe anaphylaxis has a short onset time with IV drugs [72]. However, future experiences could consider different safe locations.

Absolute contraindications

DPT should be avoided on patients who have experienced severe, life-threatening immunocytotoxic reactions, vasculitic syndromes, exfoliative dermatitis, erythema multiforme major/Stevens-Johnson syndrome, drug-induced hypersensitivity reactions (with eosinophilia)/DRESS, and toxic epidermal necrolysis.

Patients who do not need any further treatment with the suspected antineoplastic drug or who are going to swift to an alternative and equally effective chemotherapy scheme. To ensure complete avoidance of this error, the RCUH proposed signing of an "indication document" by the referring oncologist to ensure the patient is in need of the culprit drug and no alternatives have been reported as equally effective [20, 34].

Lack of access to adequate installations and personnel [38]: readily available well-trained medical and nurse staff, continuous monitoring of the patient's condition (and vital signs), intravenous access, and intensive care room access/emergency treatment.

Relative contraindications

Patients with previous life-threatening reaction (such as a history of intubation and cardiovascular collapse). The RCUH study [17••] found no association between severity of initial reaction and final diagnosis of hypersensitivity. However, other groups include the severity of the initial reaction as a key point in their risk assessment [38]. The severity of initial reactions may not reliably predict the result of the DPT or the severity of the reaction during a positive DPT [17••]. This is important, because we must not take security for granted with mild initial reactions. This may be because other factors may be affecting initial reaction severity, like, for example, suboptimal treatment of the initial reaction or other conditions mimicking anaphylaxis [73, 74]. In any case, DPT should be very carefully considered in patients with an initial very severe reaction, an individual risk assessment should be especially careful, and multidisciplinary discussion would be recommended. We must take into account that the patient may be reluctant to suffer another reaction, and in case of a new severe reaction, the patient may be even more reluctant for attempting desensitization [1••, 17••, 34, 38, 39]. It may be important to empower the patient and share the decision process.

Pregnant women. There have been accepted exceptions to this contraindication whenever the culprit drug may be necessary for delivery or pregnancy or to treat an active infection [38, 39, 75]. However, the mother is already accepting an important risk receiving chemotherapy during pregnancy, so the additional risk of DPT may be completely unnecessary in the very rare cases we will encounter this situation. In these cases, direct desensitization may be more reasonable.

Patients with situations or comorbidities where exposure might provoke situations beyond medical control (such as unavoidable use of beta-blockers,

mastocytosis, uncontrolled asthma or lung disease with forced expiratory volume < 1 L in 1 s).

Timing

Even if there is neither defined limit nor consensus regarding this topic, some recommendations even suggest waiting for 1 month after the DHR before performing the DPT [38]. One of the main objectives when assessing patients who react to antineoplastics or biologicals must be to ensure the patient receives the needed treatment on time, without delays [1••, 17••]. So, waiting may not be possible for these patients; moreover, many chemotherapy drugs have strict administration schemes, which should not be altered in order to avoid risks of toxicity or risk of affecting efficacy. Therefore, the patient's next scheduled treatment should be used as DPT (therefore, avoiding problems, such as delays or overdose), meaning that most patients (with some exceptions) are to be scheduled for DPT approximately 2 to 3 weeks after the initial reaction (depending on chemotherapy regimens, oncology/patient decisions, and patient individual treatments).

Drugs with very low risk of toxicity or overdosing under controlled environments, like leucovorin, may be scheduled in different previous days and then added to the standard scheme when necessary [19]. This is especially useful when different drugs need to be tested.

Protocol

Dosage of DPT may depend on different variables [38]. No international guidelines for DPT with antineoplastic and biological agents have been published, so protocols could vary locally. The RCUH DPT protocol [17••] is based on direct re-administration of the culprit drug under standard conditions (to avoid possible induction of tolerance due to lower infusion rates or intensified premedications). Most antineoplastic and biological drugs are meant to be infused for long periods, so the dose per minute is already low. The RCUH places more emphasis on ensuring an adequate controlled environment and expert drug allergy trained personnel than in the protocol. However, more cautious protocols could be designed locally, either for patients with more severe initial reactions or higher risk assessments or for any referred patient. In fact, some centers, like BWH suggests a cautious step-wise approach for taxane-reactive patients, with the equivalent to DPT ("challenge") situated as a possibility after tolerated desensitizations [34]. Local variations, such as this one, could be useful for centers with lower referral of patients, which may find problems to rapidly organize the necessary safety measures for a DPT at the time of first referral, but can afford overload by "unnecessary" cautious desensitizations and later program a formal DPT.

Concomitant drugs

Beta-blockers and probably ACE inhibitors, according to some authors, might need to be held prior to the procedure [34, 38].

To keep standard regimes unaltered, additional required medications (other antineoplastics, leucovorin, etc.) should be also administered as prescribed by the referring physician. If more than one chemotherapeutic drug was possibly involved in an immediate DHR, and they need to be administered in the same day (consultation with oncologist is needed), these DPTs could be performed on the same day, but separating both drugs as much as possible. When the initial DHR is a delayed one, separation is recommended to ensure a rapid and certain diagnosis.

Whenever needed, provocations with other non-cytotoxic drugs, such as premedications, concomitant drugs possibly involved in the initial reactions were performed before DPT with the culprit drug [1••, 19].

Interpretation of the results

DPT was considered positive when it reproduced the original symptoms or showed an objective DHR [1••, 17••, 38].

Restart protocol

It is paramount that the patient does not miss or alter chemotherapy regimes in order to perform a DPT. Therefore, in case of a positive DPT, once symptoms are controlled after adequate treatment and the patient is

asymptomatic, the infusion may be immediately (approximately within 30 min after the DHR) restarted at a quarter of the final infusion rate for 15 min, and then increased to half of the initial infusion rate until all the medication was administered ("restart protocol"), and the excellent safety profile of this approach was studied by Alvarez-Cuesta [17••].

Follow-up

Patients with a negative DPT are eligible to continue with standard administrations. However, some patients, especially platin-reactive patients, may need follow-up during the next administrations, including preventive ST [17••, 28, 70]. Platin-reactive patients in whom a period over 6 months has passed between initial reaction and allergy workup are suspected to be experiencing a negativization of ST, and may be experiencing resensitization [17••, 30, 39], similar to what has been observed with betalactams [39]. 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

It is still quite common to find in many centers "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), and we even find reports of patients being subjected to re-exposures without an adequate systematic allergy workup [76]. These practices must be emphatically discouraged and institutionally blocked, in order to ensure patient's safety. These practices may entail unnecessary risks, may even account for deaths [77], and may result in the missing of many important data that we could have collected in an allergy-controlled environment. Multidisciplinary institutional teams lead by allergists are the key for avoiding these risks.

Conclusions

Allergy departments are experiencing an increasing demand of drug allergy assessment, including atypical drugs such as chemotherapy and biologicals. Clinical history alone is an unreliable indicator of true hypersensitivity and a suboptimal method for risk assessment. A misdiagnosis could lead to terrible consequences for the patient. For all these reasons, the standard approach for drug allergy should be contemplated also for these drugs: clinical history, risk assessment, skin testing, in vitro techniques, drug provocation testing, de-labeling/desensitization. Dedicated drug multidisciplinary drug desensitization programs/units, with dedicated space for their activity, throughout the globe have demonstrated their proficiency in the successful management of these drugs, continuous improvement and innovation, and this type of team-work approach should be encouraged.

Compliance with Ethical Standards

Conflict of Interest

Ricardo Madrigal-Burgaleta, Paula Vazquez-Revuelta, Jaume Marti-Garrido, Ramon Lleonart, Runa Ali, and Emilio Alvarez-Cuesta declare no conflicts of interest relevant to this manuscript.

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.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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