

A Large Single-Hospital Experience Using Drug Provocation Testing and Rapid Drug Desensitization in Hypersensitivity to Antineoplastic and Biological Agents



Ricardo Madrigal-Burgaleta, MD, PhD*, Lorena Bernal-Rubio, MD*, Maria Pilar Berges-Gimeno, MD, PhD,
Laura Victoria Carpio-Escalona, MD, Patricia Gehlhaar, MD, and Emilio Alvarez-Cuesta, MD, PhD *Madrid, Spain*

What is already known about this topic? Rapid drug desensitization (RDD) is a cost-effective technique that enables hypersensitive patients to receive their first-choice treatments. RDD shows optimal results when managed within a multidisciplinary team.

What does this article add to our knowledge? This experience allows us to describe general management plans, as well as specific patient phenotypic patterns, predictors for reactions, and risk considerations that need a tailored approach (taking into account the 3 prominent drug categories: platins, taxanes, and biologicals).

How does this study impact current management guidelines? Use of the current diagnostic and therapeutic approach may be valuable in other settings to optimize the management of hypersensitivity to taxanes, platins, and biologics.

BACKGROUND: Large-scale studies of drug provocation testing (DPT) or rapid drug desensitization (RDD) for hypersensitivity to antineoplastics and biologicals are scarce and limited to a few institutions.

OBJECTIVE: Our aim was to review our experience with DPT and RDD in a large number of patients with a history of hypersensitivity to antineoplastics and biologicals and summarize the practical implications of that experience.

METHODS: This was a 7-year prospective, observational, longitudinal study with reactive patients referred to the Desensitization Program at Ramon y Cajal University Hospital (RCUH). Patients were selected after following our systematic and validated diagnostic approach (clinical history, skin test, risk assessment, specific IgE, DPT) before RDD. Candidate patients underwent RDD using the RCUH protocol. Cetuximab reactors underwent 1-bag RDDs.

RESULTS: A total of 1027 intravenous RDDs were performed using the RCUH protocol (399 platins, 395 taxanes, 178 biologicals, 55 other drugs), and 1026 were successfully accomplished in the 186 patients (of 515 referred patients) who met inclusion criteria for RDD. No breakthrough reactions

occurred in 88% of RDDs. Most breakthrough reactions were mild. A total of 341 DPTs were performed, and 229 results were negative (67%). DPTs helped exclude hypersensitivity in 44% (229 of 515) of referred patients. In addition, 77 one-bag RDDs were performed in 6 cetuximab-reactive patients.

CONCLUSIONS: This experience allows us to describe general management plans, as well as specific patient phenotypic patterns, predictors for reactions, and risk considerations that need a tailored approach (taking into account the 3 prominent drug categories: platins, taxanes, and biologicals). © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:618-32)

Key words: Drug allergy; Desensitization; Oxaliplatin; Paclitaxel; Rituximab; Chemotherapy; Biologicals; Skin test; Drug provocation test; Specific IgE

INTRODUCTION

Recent reports show an increase in the diagnosis of neoplastic and inflammatory diseases, and a widening range of therapeutic options that positively affect survival.^{1,2} This implies that a larger number of patients are exposed to the use of antineoplastic and biological agents for longer periods of time; thus, drug hypersensitivity reactions (DHRs) to these drugs have been reported with increasing frequencies.³

These DHRs may be severe; in fact, antineoplastic agents have been reported to be the third leading cause of fatal drug-induced anaphylaxis in the United States.⁴ These severe DHRs may jeopardize first-choice treatments in reactive patients and affect survival prognosis, so appropriate management of this problem is becoming essential.⁴⁻¹³

Rapid drug desensitization (RDD) is the cornerstone of the therapeutic approach to DHRs and enables reactive patients to

Allergy Division, Ramon y Cajal University Hospital, Madrid, Spain

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Corresponding author: Ricardo Madrigal-Burgaleta, MD, PhD, Hospital Universitario Ramon y Cajal, Servicio de Alergia, Ctra Colmenar Viejo km 9, 100, 28034 Madrid, Spain. E-mail: ricardo.madrigal.md.phd@gmail.com.

* These authors share first-author credit.

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Abbreviations used

DHRs- drug hypersensitivity reactions
DPT- drug provocation testing
RCUH- Ramon y Cajal University Hospital
RDD- rapid drug desensitization
SPT- skin prick test
ST- skin testing

receive their first-choice treatment in spite of their hypersensitivity. RDD is a cost-effective technique that positively affects survival in these patients, and it shows optimal results when managed by multidisciplinary teams led by expert allergists in close collaboration with oncologists, nurses, and pharmacists.⁵⁻¹⁴

The Ramon y Cajal University Hospital (RCUH) validated a new short RDD protocol.⁷ Subsequently, data on a larger cohort of patients validated diagnostic tests before RDD, namely, skin testing (ST), oxaliplatin-specific IgE, and drug provocation test (DPT).^{5,6}

The fundamental objective of this study was to report the findings obtained from the analysis of the large RCUH cohort of strictly studied patients (ie, diagnostic protocol including systematic DPT) to identify generalizable lessons from this experience. On the basis of the data obtained, we also aimed for additional monitoring of our patient management procedures (Table I), of our standard of practice (Figure 1), and of the RCUH RDD protocol (Table II). In addition, on the basis of the data obtained, we aimed to propose possible general algorithms with predictive (biomarkers, phenotypic patterns, check lists), diagnostic/therapeutic (flow charts), safety/prevention, and classification approaches, while highlighting differences between the 3 major drug categories (platins, taxanes, and biologicals).

METHODS

Informed consent statement

The RCUH Ethics Committee approved the study protocol and informed consents.

Study population and design

Prospective, observational, longitudinal study with the patients who, during a 7-year period (between January 2010 and January 2017), suffered DHRs to antineoplastic or biological agents at RCUH and were referred to the Allergy Division Desensitization Program.

Initial reaction

Initial DHRs were classified into 2 groups²⁴: immediate DHRs (occurring during drug infusion or within 1 hour after finishing) and nonimmediate DHRs (>1 hour after finishing drug infusion). See Figure 1. We classified patients according to 3 different severity classifications: National Cancer Institute Common Toxicity Criteria¹⁵; Brown¹⁶; and the RCUH classification, which was adapted from previous international severity classifications.¹⁶⁻²⁰ See Table I.

Risk assessment

Patients were classified as high-risk or medium/low-risk,⁵⁻¹³ as further explained in Table I.

Diagnostic protocol: ST and DPT

Trained personnel in adequate settings performed and assessed ST according to international methodology on all referred patients.⁵⁻¹³

DPT is the controlled administration of a drug to study DHRs, and it is considered to be the criterion standard to establish or exclude the diagnosis of hypersensitivity.^{5,25} Methodology for DPT with antineoplastic and biological agents is explained in recent articles by our group.^{5,13} Patients were offered the possibility of undergoing DPT in a multidisciplinary discussion based on the benefits for the patient and a safety-first policy. The patient was empowered to make the final decision by considering 2 fundamental decision pillars: (1) data on indication for treatment from the referring physician, and (2) data on risk assessment from the allergist.

DPTs with other drugs such as premedications, concomitant drugs,⁶ or additional antineoplastic or biological agents possibly involved in the initial reactions were performed before DPT with the culprit drug.

Diagnostic protocol: Criterion standard in this study

Clinical history alone cannot be accepted as criterion standard. As has been observed for nonsteroidal anti-inflammatory drugs,²⁶ symptoms or “unequivocal” clinical history alone may not lead to a true diagnosis. We have observed^{5,12} that “unequivocal clinical history” was a very poor diagnostic tool for hypersensitivity to oxaliplatin, with a specificity of 4% (95% CI, 3.7%-11.7%), and a positive predictive value of 62.5% (95% CI, 50.6%-74.4%). Thus, further allergy workup by experts is essential to reach a confirmatory diagnosis and a safe therapeutic approach.

An unequivocal clinical history was not considered optimal as a criterion standard for a positive diagnosis of hypersensitivity, but patients needed to also show positive ST result and/or positive DPT result and/or positive specific IgE. However, the criterion standard for a negative diagnosis of hypersensitivity was strictly limited to showing a negative DPT result. Patients who could not meet criteria for a positive or negative diagnosis were considered inconclusive.

Candidate patients for RDD

We considered candidates for RDD those patients who met the following inclusion criteria: (1) DHR during drug infusion (or within 48 hours); (2) referring physician confirmed indication and need of treatment with the culprit drug as a first choice; (3) signed informed consents; and (4) positive diagnostic protocol (or, alternatively, a high-risk assessment).

Regarding “(2)”: As a patient safety measure,^{5-13,21-23} to provide patients with multidisciplinary, coordinated, and empowered decisions, an additional informed consent confirming indication for treatment with the culprit drug as first-choice drug (signed both by patients and by referring physicians) was requested.

Patients with a negative diagnostic protocol (negative DPT result) were not candidates for RDD and continued with their regular chemotherapy sessions (hypersensitivity was ruled out). Patients who did not give their consent for RDD or who did not need treatment with the culprit drug were not candidates for RDD. Patients with late reactions occurring beyond 48 hours after infusion, severe immunocytotoxic reactions, vasculitis, bullous skin diseases (eg, Stevens-Johnson syndrome/toxic epidermal necrolysis, or drug reaction with eosinophilia and systemic symptoms/drug-induced hypersensitivity syndrome) were excluded from RDD.^{5-14,25,27}

The RCUH RDD protocol

The RCUH standard 10-step RDD protocol is designed to last approximately 4 hours (therefore allows for single-morning RDDs). It is compliant with safety measures for handling hazardous drugs, and valid for different drugs and for different types of immediate reactions (IgE-dependent and IgE-independent).⁷

TABLE I. RCUH classification for DHRs to chemotherapy and biological agents, and management either during DPTs or during RDD

I. Mild reaction	II. Moderate reaction	III. Severe reaction	IV. Anaphylactic shock
Erythema Pruritus Local urticaria/angioedema Fever/chills (<38°C) Mild back pain	-Slow onset (>15 min): Generalized urticaria/angioedema Coryzal symptoms Irritative cough Dyspnea (SpO ₂ > 92%) Throat tightness Nausea Abdominal pain Severe back pain Fever (>38°C)	-Rapid onset (<15 min) General urticaria/angioedema Coryzal symptoms Irritative cough -and/or manifestation of Throat tightness with dysphagia and/or dysphonia and/or stridor Wheezing Chest tightness Vomiting Diarrhea SpO ₂ < 92% Diaphoresis Dizziness Hypertension	-Immediate onset (or rapid progression) of any of the latter and manifestation of any of the following: Hypotension Cyanosis Sense of impending doom Faintness Loss of sphincters control Cardiovascular and/or respiratory arrest
Stop the infusion immediately Call for help and contact Emergency Team <i>Vital signs (blood pressure, heart rate, respiratory rate, SaO₂, T°). Tryptase 60-90 min after DHR onset. If available: IL-6</i>			
When meeting anaphylaxis criteria: administer F. Can be repeated every 5 min			
Consider A (in RDD or fastly self-limiting), B, C (if angioedema or fever), J (fever or pain), K (if flushing)	Consider D, E, J (fever or pain), K (flushing), M (severe pain)	Consider the previous and also G and L (respiratory symptoms predominantly)	Consider the previous and H (if hypotension), and I (refractory or severe symptoms)
DHR during DPT management		Whenever possible activate Restart Protocol: Once symptoms are controlled and the patient is asymptomatic (approximately within 30 min after the DHR), the infusion may be immediately restarted at 1/4 of the initial infusion rate for 15 min, and then increased to 1/2 of the initial infusion rate until all the medication is administered ⁵	
DHR during RDD management		Once symptoms are controlled and the patient is asymptomatic (approximately within 30 min after the DHR) restart on the same step the breakthrough reaction appeared ⁷	
Patients were classified as high-risk (ie, presence of patient-related factors or life-threatening reaction) or medium/low-risk. But the optimal risk-assessment will depend on several factors. The allergist must be very aware of all these factors to make a sensible assessment, namely:		(1) Patient-related: Comorbidities where exposure might provoke situations beyond medical control (such as uncontrolled asthma or lung disease with FEV₁ < 1 L, or unavoidable use of β-blockers, mastocytosis, etc) (2) DHR-related: Previous life-threatening reaction (such as a history of intubation and cardiovascular collapse), type of reaction (immediate, nonimmediate, etc) (3) Exceptional situations like pregnancy, acute infections, or critically-ill patients (4) Institutional-related factors: Access to expert allergists with clinical expertise in drug allergy, access to a multidisciplinary team approach for each individual patient, specialty-trained personnel, specific resources, appropriate facilities (special areas for these techniques, and access to MICU beds), risk-management strategies and worst-case scenario recovery plans (5) Allergy workup risk markers (ST, specific IgE, tryptase, etc)	
RCUH classification rationale: We found that oncology-focused classifications ¹⁵ were impractical for adequately grading the clinical relevance or ensuring adequate management of immediate DHRs. However, other allergy-focused classifications ¹⁶ normally used for assessing these DHRs may be too simplistic and leave out important features (eg, fever/chills) that may need adaptations. ⁵ We found a new specific classification necessary to ensure optimal risk-assessment. Taking into account the special clinical spectrum of DHRs to antineoplastics and biologicals, as well as other factors that are considered important to grade the severity of a reaction (elapsed time to onset, etc) in previous international classifications for anaphylaxis and hypersensitivity reactions, ¹⁶⁻²⁰ we designed the RCUH classification, which became a useful tool for standard classification and management of DHRs to antineoplastics and biologicals at our hospital (whether facing an initial reaction, a positive DPT result, or breakthrough reactions during RDD).			

ASA, Acetylsalicylic acid; MICU, medical intensive care unit; NSAID, nonsteroidal anti-inflammatory drug.

A. No medication; 30-min observation to monitor symptoms progression; B. Oral antihistamines; C. Oral corticosteroids; D. Parenteral antihistamines (intramuscular or intravenous); E. Parenteral corticosteroids (intramuscular or intravenous); F. Intramuscular adrenaline; G. Oxygen therapy and bronchodilators; H. Fluid therapy (crystalloids); I. Intravenous adrenaline, vasoactive drugs, glucagon (if beta-blockers), crash cart, etc; J. NSAIDs; K. ASA if flushing; L. Montelukast if respiratory symptoms; M. Opioids if severe pain.

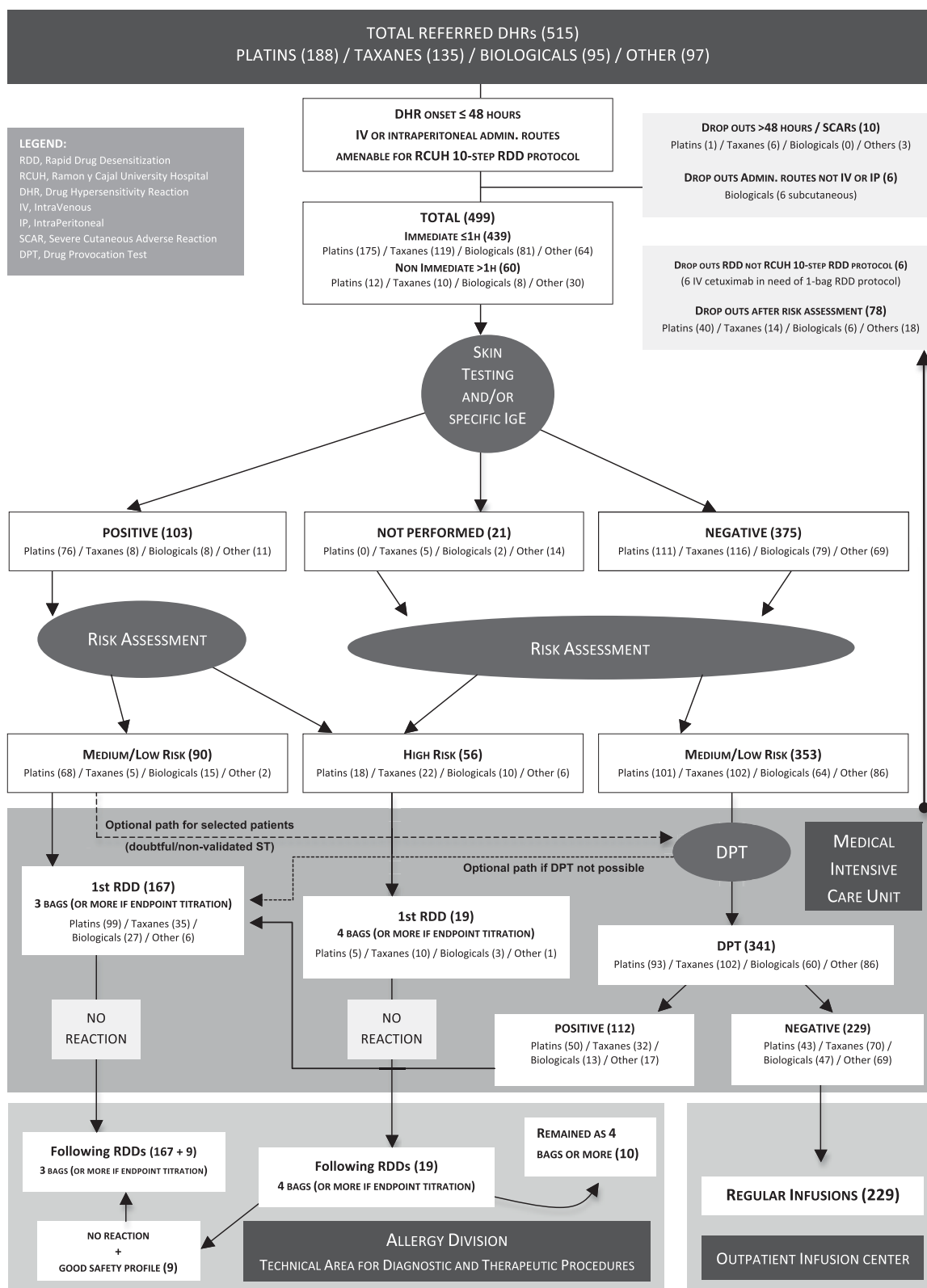


FIGURE 1. Seven years experience of RDD in our Desensitization Program at RCUH with our standard 10-step protocol: patient flowchart. *DHR*, drug hypersensitivity reaction; *DPT*, drug provocation test; *IP*, intraperitoneal; *IV*, intravenous; *RCUH*, ramon y cajal university hospital; *RDD*, rapid drug desensitization; *SCAR*, severe cutaneous adverse reaction.

TABLE II. RCUH standard rapid desensitization protocol adapted for a total dose of 600 mg of rituximab diluted in a volume of 500 mL of saline solution 0.9% and meant to be infused in 2 h

Total dose	600 mg	Solution concentration	Total dose in each solution (mg)	Drug
Solution A	500 mL	0.024 mg/mL	12	Rituximab
Solution B	500 mL	0.24 mg/mL	120	Rituximab
Solution C	500 mL	1.2 mg/mL	600	Rituximab

Step	Solution	Rate (mL/h)	Administered volume (mL)	Time (min)	Administered dose (mg)	Fold increase per step	Approximative cumulative dose infused (mg)
1	A	88	22	15	0.0	NA	0.0
2	A	100	25	15	0.6	NA	0.6
3	A	200	50	15	1.2	×2	1.8
4	A	400	100	15	2.4	×2	4.2
5	B	88	22	15	0.0	NA	4.2
6	B	100	25	15	6.0	×2.5	10.2
7	B	200	50	15	12.0	×2	22.2
8	B	400	100	15	24.0	×2	46.2
9	C	88	22	15	0.0	NA	46.2
10	C	150	37.5	15	45.0	×1.9	91.2
10'	C	212	424	120	508.8	×1.4	600.0

Total infusion time: 270 min (4.5 h).

Premedications: Ideally they should comply with the manufacturer's instructions and institutional protocols for standard rituximab infusion. In addition, tailored premedication may be added, as explained in the Methods section (eg, montelukast and acetylsalicylic acid).

Total dose calculation and discarded volume: Not all the volume in solutions A, B, or C is infused. We start the protocol with solution A containing a 1/50 dilution, then solution B with a 1/5 dilution, and we end with a final solution C containing a full concentration of the culprit drug. Total dose to be infused during solution C is calculated by subtracting the cumulative dose administered in steps 1-8 from the total desired dose.

Adjustments to the volume of the bags: The standard volume in the solution bags for the RCUH RDD protocol is 250 mL.^{7,13} But in cases such as this, bag volume might need adjustment depending on manufacturer's instructions (eg, increase solution bag to 500 mL when exceeding certain doses of paclitaxel).

Additional bags for high-risk patients: Whenever needed in high-risk patients, additional solutions with lower concentrations than solution A may be added before solution A to ensure a more cautious starting dose, and whenever possible as determined on the basis of an end-point titration according to local protocols (in case of positive skin test results).

Flushing steps: Each solution uses an individual infusion line previously primed with 22 mL of the dilutor substance. Steps 1, 5, and 9 are considered "line flushing steps" (in which 22 mL of the dilutor substance is administered).

Adjustments to final infusion rate: Step 10 may be adapted to the desired final infusion rate according to the standard regimes indicated by the referred oncologist (additional steps may be added to reach higher infusion rates while maintaining a maximum dose increasing by 2-fold to 2.5-fold with each step).

Avoiding human errors: Infusion pumps with automatic multistep infusion options (Alaris SE double channel) were used to avoid human errors associated with manually changing infusion rates every 15 min.^{7,21-23} We used 22 mL infusion systems for these pumps (Alaris SE I pump smartsite infusion set).

NA, Not applicable.

Unresponsiveness to the culprit drug is achieved by administering 2-fold to 2.5-fold incremental doses of the drug antigen at fixed 15-minute time intervals. The rationale for gradually (2-fold to 2.5-fold) increasing doses in a step-wise manner without reaching a threshold capable of triggering anaphylaxis is based on IgE/antigen mast cell desensitization *in vitro* data.^{4,28-32}

The RCUH RDD protocol uses 3 drug dilutions with increasing drug concentrations, which are administered consecutively. However, this flexible protocol may be individualized depending on risk assessment, specific dose needs, special infusion protocols, breakthrough reactions during RDD, and so forth. See Table II.

RDD premedication, concomitant drugs, timing, and location

Only standard premedications for each drug (according to prescribing information by the manufacturer and institutional protocols) were normally used. Some cases might need additional

premedication customized to their initial or breakthrough reactions: Benzodiazepines are used to relieve anxiety; acetylsalicylic acid 500 mg orally and montelukast 10 mg orally administered 2 days before the RDD may be used to address cutaneous and respiratory symptoms like flushing or bronchospasm^{7,33}; and other nonsteroidal anti-inflammatory drugs, corticosteroids, and opioids before or during RDD may help in controlling fever/chills or pain.¹⁴ We avoided the systematic use of additional corticosteroids (unless prescribed for other reasons like antiemetic therapy), given that previous data show that they fail to effectively ameliorate breakthrough reactions when compared with acetylsalicylic acid/montelukast premedication.³³ Moreover, whenever possible, we avoided the systematic use of additional antihistamines, because in our experience they may mask mild cutaneous signs and symptoms, which are usually early-onset warning alarms for breakthrough reactions.¹³

Whenever possible, "b-blockers were held for 24 h prior to desensitization, because of their possible interference with the

TABLE III. Identifying factors acting as predictors of a hypersensitivity diagnosis and/or as predictors of breakthrough reactions during RDD**Taxanes: Factor associated with a hypersensitivity diagnosis***Analyzed initial variables that showed no association to a diagnosis of hypersensitivity*

Severity (Brown), severity (NCI), severity (RCUH), age, sex, atopy, type of cancer/disease, confirmed drug allergy, serum baseline tryptase, "re-treatment," any cutaneous symptoms, urticaria, erythema/flushing, angioedema, pruritus, maculopapular rash, any neuromuscular symptoms, dysesthesia, paresthesia, myodesopsia, dysgeusia, lumbar pain, cramps, blurry vision, disorientation, tinnitus, hallucinations, weakness, any respiratory symptoms, rhinoconjunctivitis, dyspnea/shortness of breath, cough, wheezing, cyanosis, respiratory arrest, any gastrointestinal symptoms, nausea, vomiting, diarrhea, bloating, chest pain, presyncope, syncope, hypotension, palpitations, dizziness, cardiac arrest, any ENT symptoms, dysphonia, throat tightness, fever/chills, dyaphoresis

Analyzed initial variables that did show association to a diagnosis of hypersensitivity in the univariate analysis

Initial factor	P value	Initial factor	P value
Previous reactions	.011	Sense of impending doom	.01
O ₂ desaturation	<.001	Hypertension	.018
Any cardiovascular symptoms	.005	Elapsed time from drug administration to reaction onset	<.001
Tachycardia	.017	Total IgE	.042

Final predictors of a diagnosis of hypersensitivity after multivariate analysis

Initial factor	Final diagnosis	RRR	95% CI	P value
Any cardiovascular symptoms	Inconclusive	3.46	1.21-12.28	.002
O ₂ desaturation	Inconclusive	1.54	1.02-2.65	.04
Elapsed time	Negative	1.85	1.26-7.47	.003

Platins: Factor associated with a hypersensitivity diagnosis*Analyzed initial variables that showed no association to a diagnosis of hypersensitivity*

Severity (Brown), severity (NCI), severity (RCUH), age, sex, type of cancer/disease, atopy, confirmed drug allergy, serum baseline tryptase, urticaria, angioedema, maculopapular rash, any neuromuscular symptoms, dysesthesia, paresthesia, myodesopsia, dysgeusia, lumbar pain, cramps, blurry vision, disorientation, tinnitus, hallucinations, weakness, any respiratory symptoms, rhinoconjunctivitis, dyspnea/shortness of breath, cough, wheezing, cyanosis, respiratory arrest, nausea, vomiting, diarrhea, bloating, any cardiovascular symptoms, chest pain, tachycardia, sense of impending doom, presyncope, syncope, hypertension, hypotension, palpitations, dizziness, cardiac arrest, any ENT symptoms, dysphonia, throat tightness, fever/chills, dyaphoresis.

Analyzed initial variables that did show association to a diagnosis of hypersensitivity in the univariate analysis

Initial factor	P value	Initial factor	P value
Previous reactions	<.001	O ₂ desaturation	.007
Re-treatment	.003	Any gastrointestinal symptoms	.042
Any cutaneous symptoms	.011	Elapsed time from drug administration to reaction onset	<.001
Erythema/flushing	.001		
Pruritus	.021	Total IgE	<.001

Final predictors of a diagnosis of hypersensitivity after multivariate analysis

Initial factor	Final diagnosis	RRR	95% CI	P value
Previous reactions	Positive	16.65	5.27-52.72	<.001
Total IgE	Positive	1.46	1.00-2.45	.039

Factors associated with breakthrough reactions in RDD patients*Analyzed factors that showed no association to the presence of breakthrough reactions during RDD*

(continued)

TABLE III. (Continued)

Factors associated with breakthrough reactions in RDD patients				
Culprit drug, SPT, ID, oxaliplatin-specific IgE, multiple severity variables (all classifications Brown, NCI, RCUH, and for both initial reaction and DPT whenever positive), age, sex, type of cancer/disease, atopy, confirmed drug allergy, previous reactions, elapsed time from drug administration to initial reaction onset, total IgE, serum baseline tryptase, re-treatment, multiple symptoms variables (all of the above symptoms variables for both initial reaction and DPT whenever positive)				
<i>Analyzed initial factors that did show association to RDD breakthrough reactions in the univariate analysis</i>				
Initial factor	P value	Initial factor	P value	
SPT	.033	Atopy	.044	
<i>Final predictors of RDD breakthrough reactions after multivariate analysis</i>				
Initial factor	Breakthrough reactions	RRR	95% CI	P value
SPT (positive)	Reactive	4.01	1.76-10.34	.01
Atopy	Reactive	2.16	1.59-14.06	.03

ENT, Otorhinolaryngology; ID, intradermal; NCI, National Cancer Institute.

“Re-treatment” (starting new treatment with an antineoplastic drug the patient had previously received for a period over 12 mo); “previous reactions” (generally historical unnoticed/overlooked mild reactions during previous administrations of the same culprit drug before the initial reaction); elapsed time from drug administration to reaction onset is a continuous variable (in the univariate analysis, the direction of the relationship was for longer elapsed times to be associated with a negative diagnosis).

therapeutic effect of epinephrine.³⁴ To keep standard regimes unaltered, additional required medications (other antineoplastics, leucovorin, etc) were also administered as prescribed by the referring physician. The patient's next scheduled treatment was used for RDD (avoiding therefore problems such as delays or overdose), meaning that most patients (with some exceptions) were to be scheduled for RDD approximately 1 to 3 weeks either after the initial reaction or after positive DPT result (depending on chemotherapy regimens and patient individual treatments, characteristics, and study protocol). Because RDD induces a temporary tolerance and these treatments usually have 1- to 3-week intervals between them, candidate patients needed to receive all following treatments by means of RDD. First, RDDs were conducted in medical intensive care unit beds assigned to the desensitization program. Once RDDs were successfully tolerated in medical intensive care unit beds, the following RDDs were conducted in a semi-intensive care room with beds designed for and dedicated to our high-complexity patients, which is included in the Technical Area for Diagnostic and Therapeutic Procedures of our Allergy Division. This area has specific resources for these procedures, with 1:2 nurse:patient ratio, bedside physical presence of an allergist with a 1:4 allergist:patient ratio, hazardous drugs handling measures (waste and spilling management, protection equipment, etc), constant monitoring, crash cart, less than 1 min medical intensive care unit access, and so forth.

Cetuximab

As has been previously stated,³⁵ cetuximab “is distributed at a fixed concentration in a proprietary buffer solution and, because the buffer is not available as a stand-alone product.” Our Pharmacy Department found it difficult to guarantee product stability when diluting cetuximab in saline solutions. Thus, for cetuximab RDDs, we used the 1-bag 5-step protocol published by Hong et al.³⁵

RDD Breakthrough reactions

Management of breakthrough reactions is explained in Table I. If a patient suffered a breakthrough reaction during RDD, the next RDD was individualized accordingly to symptoms, severity, tryptase during reaction, new ST, and new specific IgE. Measures included additional customized premedications (according to type of reaction, as explained above), decelerating dose escalation with intermediate infusion steps, administering prophylactic medication before reactive steps, additional solutions before solution A (according to ST titration or risk assessment), temporary final dose reduction, or pretreatment with omalizumab.³⁶ Whenever facing a RDD breakthrough reaction, we kept in mind that other drugs such as premedications, concomitant drugs, or additional antineoplastic or biological agents may possibly be involved, and may need further study before the next RDD.⁶

Statistical analysis

We studied possible associations between factors from the initial patient characteristics and the results of their hypersensitivity diagnosis according to the previous criterion standard (positive, negative, or inconclusive). In addition, we studied possible factors that could act as predictors of breakthrough reactions during RDD.

To identify variables associated with a confirmed hypersensitivity diagnosis, we selected our 2 different groups with the largest sample size and specific hypersensitivity phenotype (“taxanes” and “platins”), and we performed separate analysis for each of them. “Biologicals” and “others” had to be excluded from this focused drug-specific analysis given the heterogeneity of the data in those

TABLE IV. Characteristics of the 515 patients referred to our Desensitization Program at the RCUH over a 7-y period, and features of their initial reactions

Characteristic	No. of patients (%)
Culprit drug	
Platins	188 of 515 (37)
Oxaliplatin	142 of 188 (76)
Carboplatin	40 of 188 (21)
Cisplatin	5 of 188 (3)
Taxanes	135 of 515 (26)
Paclitaxel	123 of 135 (91)
Docetaxel	9 of 135 (7)
Nab-paclitaxel	3 of 135 (2)
Biological agents	95 of 515 (18)
Rituximab	32 of 95 (34)
Infliximab	10 of 95 (11)
Cetuximab	10 of 95 (11)
Natalizumab	7 of 95 (7)
Trastuzumab	7 of 95 (7)
Bevacizumab	6 of 95 (6)
Bortezomib	6 of 95 (6)
Pertuzumab	5 of 95 (5)
Adalimumab	4 of 95 (4)
Certolizumab	2 of 95 (2)
Anakinra	1 of 95 (1)
Golimimumab	1 of 95 (1)
Alentuzumab	1 of 95 (1)
Etanercept	1 of 95 (1)
Other drugs	97 of 515 (19)
Leucovorin	28 of 97 (29)
Irinotecan	25 of 97 (26)
Cyclophosphamide	12 of 97 (12)
Gemcitabine	12 of 97 (12)
Liposomal doxorubicine	4 of 97 (4)
Etoposide	4 of 97 (4)
5-Fluorouracil	1 of 97 (1)
Azacitidine	1 of 97 (1)
Bleomycin	1 of 97 (1)
Capecitabine	1 of 97 (1)
Everolimus	1 of 97 (1)
Lenalidomide	1 of 97 (1)
Lenogastim	1 of 97 (1)
Trabectedin	1 of 97 (1)
Vandetanib	1 of 97 (1)
Triptorelin	1 of 97 (1)
Vinorelbine	1 of 97 (1)
Iphosphamide	1 of 97 (1)
History of atopy	142 of 515 (28)
History of confirmed drug allergy	60 of 515 (12)

Clinical features and severity of initial reactions*

Characteristic	Platins (n = 188)	Taxanes (n = 135)	Biologicals (n = 95)	Other (n = 97)
Symptoms (%)				
Cutaneous	79	85	75	88
Cardiovascular	32	41	24	21
Respiratory	40	51	36	22

(continued)

TABLE IV. (Continued)

Characteristic	Platins (n = 188)	Taxanes (n = 135)	Biologicals (n = 95)	Other (n = 97)
Gastrointestinal	29	16	22	24
Neuromuscular	19	39	19	8
Fever/chills	20	9	35	36
ENT	20	22	25	10
Severity (Brown), n of N (%)				
Grade 1	79 of 188 (42)	27 of 135 (20)	36 of 95 (38)	40 of 97 (41)
Grade 2	64 of 188 (34)	73 of 135 (54)	35 of 95 (37)	38 of 97 (39)
Grade 3	45 of 188 (24)	35 of 135 (26)	24 of 95 (25)	19 of 97 (20)
Severity (RCUH)				
Grade I	72 of 188 (38)	27 of 135 (20)	36 of 95 (38)	40 of 97 (41)
Grade II	40 of 188 (21)	22 of 135 (16)	26 of 95 (27)	25 of 97 (26)
Grade III	60 of 188 (32)	67 of 135 (50)	23 of 95 (24)	27 of 97 (28)
Grade IV	16 of 188 (9)	19 of 135 (14)	11 of 95 (12)	5 of 97 (5)

ENT, Otorhinolaryngology.

Atopy (allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic dermatitis, or food allergy) was measured by skin test to a standard battery of 17 common inhalant aero-allergens (including pollens, house dust mites, molds, animal danders, profilin, peach lipid transfer protein) and specific allergens according to patient clinical history.

*No. of patients presenting with a certain characteristic: Given that some patients may present with different symptoms, the total percentages may exceed 100% to account for all of these.

groups (mainly because of the many different drugs and phenotypes in those groups).

For each group (taxanes and platins), univariate analysis was used for determining significant associations between this study's diagnostic protocol criterion standard (positive, negative, inconclusive) and the relevant clinical history/initial reaction variables. For categorical variables, the Pearson chi-square test was performed. For continuous variables, ANOVA test was performed provided normality and homogeneity of variances were confirmed applying Bartlett test. A *P* value of less than .05 was considered significant. The software used for this task was Stata® 13, developed by StataCorp (College Station, Texas).

To identify variables associated with the presence of breakthrough reactions during RDD, we analyzed all patients who underwent RDD regardless of the culprit drug. We added to those previous anamnesis/initial reaction variables all the relevant results of the allergy workup (culprit drug, skin prick test [SPT], ID, symptoms and severity during DPT, oxaliplatin-specific IgE), and we used the same univariate analysis to compare all those variables (anamnesis/initial reaction plus allergy workup) with the presence or absence of RDD breakthrough reactions.

After all univariate analyses were completed, multivariate analysis with multinomial logistic regression with a backward strategy (applying the Bonferroni correction) was used to confirm the importance of the univariate possible associations and to identify independent predictors of a hypersensitivity diagnosis and/or of the presence of breakthrough reactions during RDD. The outcome in the multivariable analysis was a 3-level outcome: positive, negative, and inconclusive. See Table III.

TABLE V. Characteristics of the 186 candidate patients who underwent RDD by the standard RCUH 10-step protocol over a 7-y period, and features of their initial reactions as well as breakthrough reactions (in addition, data of 6 cetuximab 1-bag RDD candidates during that same period of time)

186 patients undergoing RDD by means of the standard 10-step RCUH protocol					
Characteristic	No. of patients (%)			No. of RDDs (%)	
Culprit drug					
Platins	104 of 186 (56)			399 of 1027 (39)	
Oxaliplatin	85 of 104 (82)			347 of 399 (87)	
Carboplatin	17 of 104 (16)			46 of 399 (12)	
Cisplatin	2 of 104 (2)			6 of 399 (2)	
Taxanes	45 of 186 (24)			395 of 1027 (39)	
Paclitaxel	40 of 45 (89)			354 of 395 (90)	
Docetaxel	3 of 45 (7)			13 of 395 (3)	
Nab-paclitaxel	2 of 45 (4)			28 of 395 (7)	
Biological agents	30 of 186 (16)			178 of 1027 (17)	
Rituximab	21 of 30 (70)			130 of 178 (73)	
Infliximab	5 of 30 (17)			36 of 178 (20)	
Natalizumab	3 of 30 (10)			6 of 178 (3)	
Trastuzumab	1 of 30 (3)			6 of 178 (3)	
Other drugs	7 of 186 (4)			55 of 1027 (5)	
Leucovorin	4 of 7 (57)			15 of 55 (27)	
Irinotecan	1 of 7 (14)			18 of 55 (33)	
Cyclophosphamide	1 of 7 (14)			4 of 55 (7)	
Gemcitabine	1 of 7 (14)			18 of 55 (33)	
History of atopy				54 of 186 (29)	
History of confirmed drug allergy				25 of 186 (13)	
Clinical features and severity of initial reactions of the 186 candidates for the RCUH protocol RDD plus the 6 candidates for the 1-bag RDD protocol*					
Characteristics of initial reactions, n (%)*					
Characteristic	Platins (n = 104)	Taxanes (n = 45)	Biologicals (n = 30)	Other (n = 7)	Cetuximab (n = 6)
Symptoms					
Cutaneous	87 of 104 (84)	33 of 45 (73)	26 of 30 (87)	5 of 7 (71)	5 of 6 (83)
Cardiovascular	35 of 104 (34)	27 of 45 (60)	12 of 30 (40)	4 of 7 (57)	2 of 6 (33)
Respiratory	49 of 104 (47)	27 of 45 (60)	15 of 30 (50)	3 of 7 (43)	3 of 6 (50)
Gastrointestinal	31 of 104 (30)	9 of 45 (20)	11 of 30 (37)	3 of 7 (43)	3 of 6 (50)
Neuromuscular	21 of 104 (20)	23 of 45 (51)	8 of 30 (27)	2 of 7 (29)	4 of 6 (67)
Fever/chills	18 of 104 (17)	5 of 45 (11)	17 of 30 (57)	2 of 7 (29)	4 of 6 (67)
ENT	16 of 104 (15)	10 of 45 (22)	11 of 30 (37)	0 of 7 (0)	2 of 6 (33)
Severity (Brown)	No. (%) of patients presenting with different severities in the initial reaction				
Grade 1	43 of 104 (41)	9 of 45 (20)	10 of 30 (33)	1 of 7 (14)	1 of 6 (17)
Grade 2	38 of 104 (37)	21 of 45 (47)	12 of 30 (40)	2 of 7 (29)	3 of 6 (50)
Grade 3	23 of 104 (22)	15 of 45 (33)	8 of 30 (27)	4 of 7 (57)	2 of 6 (33)
Severity (RCUH)	No. (%) of patients presenting with different severities in the initial reaction				
Grade I	40 of 104 (38)	9 of 45 (20)	9 of 30 (30)	1 of 7 (14)	1 of 6 (17)
Grade II	24 of 104 (23)	7 of 45 (16)	11 of 30 (37)	2 of 7 (29)	1 of 6 (17)
Grade III	35 of 104 (34)	22 of 45 (49)	7 of 30 (23)	3 of 7 (43)	2 of 6 (33)
Grade IV	5 of 104 (5)	7 of 45 (16)	3 of 30 (10)	1 of 7 (14)	2 of 6 (33)
Characteristics of breakthrough reactions*					
Symptoms					
Cutaneous	37 of 104 (36)	19 of 45 (42)	10 of 30 (33)	2 of 7 (29)	2 of 6 (33)
Cardiovascular	9 of 104 (9)	5 of 45 (11)	7 of 30 (23)	2 of 7 (29)	2 of 6 (33)
Respiratory	17 of 104 (16)	8 of 45 (16)	10 of 30 (23)	1 of 7 (14)	1 of 6 (17)
Gastrointestinal	16 of 104 (15)	3 of 45 (7)	9 of 30 (30)	1 of 7 (14)	1 of 6 (17)
Neuromuscular	12 of 104 (12)	6 of 45 (13)	8 of 30 (27)	1 of 7 (14)	1 of 6 (17)
Fever/chills	9 of 104 (9)	1 of 45 (2)	5 of 30 (17)	1 of 7 (14)	1 of 6 (17)

(continued)

TABLE V. (Continued)

Characteristics of breakthrough reactions*					
ENT	8 of 104 (8)	4 of 45 (9)	3 of 30 (10)	0 of 7 (0)	0 of 6 (0)
Safety outcome	No. (%) of patients presenting with different severities in RDD breakthrough reactions				
No reaction	66 of 104 (63)	25 of 45 (55)	18 of 30 (60)	4 of 7 (57)	4 of 6 (67)
Any reaction	38 of 104 (37)	20 of 45 (44)	12 of 30 (40)	3 of 7 (43)	2 of 6 (33)
Severity (Brown)	No. (%) of patients presenting with different severities in RDD breakthrough reactions*				
Grade 1	36 of 104 (35)	20 of 45 (44)	5 of 30 (17)	2 of 7 (29)	0 of 6 (0)
Grade 2	15 of 104 (14)	7 of 45 (16)	8 of 30 (27)	0 of 7 (0)	2 of 6 (33)
Grade 3	7 of 104 (7)	3 of 45 (7)	4 of 30 (13)	1 of 7 (14)	0 of 6 (0)
Severity (RCUH)	No. (%) of patients presenting with different severities in RDD breakthrough reactions*				
Grade I	36 of 104 (35)	20 of 45 (44)	4 of 30 (13)	2 of 7 (29)	0 of 6 (0)
Grade II	12 of 104 (12)	5 of 45 (11)	10 of 30 (33)	0 of 7 (0)	1 of 6 (17)
Grade III	8 of 104 (8)	3 of 45 (7)	3 of 30 (10)	1 of 7 (14)	1 of 6 (17)
Grade IV	2 of 104 (2)	2 of 45 (4)	0 of 30 (0)	0 of 7 (0)	0 of 6 (0)

ENT, Otorhinolaryngology.

Atopy (allergic rhinitis, allergic conjunctivitis, allergic asthma, atopic dermatitis, or food allergy) was measured by skin test to a standard battery of 17 common inhalant aeroallergens (including pollens, house dust mites, molds, animal danders, profilin, peach lipid transfer protein) and specific allergens according to patient clinical history.

*No. of patients presenting with a certain characteristic: Given that some patients may present with different symptoms, and that some patients may present with different breakthrough reactions on different procedures and with different severities, the total percentages may exceed 100% to account for all of these.

RESULTS

Patient characteristics

A total of 515 patients (188 platins, 135 taxanes, 95 biologicals, 97 others) were referred to our desensitization program during a 7-year period (January 2010 to January 2017). Mean age was 60 years (ranging from 13 to 87 years). Most patients were being treated for malignancy (493 of 515), but some patients were being treated for inflammatory disorders (22 of 515). Characteristics of initial reactions in all referred patients are presented in Table IV. Diagnostic/therapeutic flowchart is shown in Figure 1.

After allergy workup and assessment, 192 patients met the inclusion criteria for RDD. Six were cetuximab-reactive patients, and their results are described separately; but 186 patients were treated with the RCUH standard 10-step RDD protocol.

In this selected group of 186 RCUH/RDD patients, mean age was 61 years (ranging from 13 to 87 years). The severity of the initial reaction was moderate to severe (Brown's grades 2-3) in 66% (123 of 186) of the patients, with only 34% (63 of 186) of the patients having suffered a mild (grade 1) initial reaction. Further characteristics are presented in Table V.

RCUH/RDD outcomes

Of 1027 intravenous RCUH/RDD undertaken, 1026 were successfully accomplished with the standard RCUH 10-step protocol. Of 186 RDD patients, 185 could receive their target dose. One patient treated with paclitaxel revoked her consent to finish the procedure after 2 breakthrough reactions during her first RDD, and rejected further attempts, even after careful risk-benefit explanations along with her oncologist (Figure 2 and Table V).

No reactions occurred in 88% of RDDs (904 of 1027). Most breakthrough reactions were mild, and no deaths occurred. A total of 137 breakthrough reactions were observed in 73 patients (39% of all RDD patients; 38 of 73 platin-reactive patients, 20 of 73 taxane-reactive patients, 12 of 73 biological-reactive patients, and 3 of 73 other-drugs-reactive patients).

Only 6 of 73 reactive patients suffered more than 1 reaction during the same RDD (3 of 6 oxaliplatin, 2 of 6 rituximab, and 1

of 6 paclitaxel), with some of them (mainly oxaliplatin-reactive patients) showing up to 3 breakthrough reactions during their early RDDs. All reactive patients suffered at least 1 breakthrough reaction during their first RDD; however, 30% of reactive patients (22 of 73) suffered breakthrough reactions during their second RDD despite protocol adjustments. Almost all these persistently reactive patients were oxaliplatin-reactive patients (13 of 17 oxaliplatin; 6 of 17 rituximab; 3 of 17 paclitaxel), and almost all their reactions were mild and eventually controlled with the protocol adjustments explained in the Methods section. Only 2 oxaliplatin-reactive patients showed persistent moderate reactions and needed premedication with omalizumab.

We observed only 2% (3 of 137) of delayed RDD breakthrough reactions. One oxaliplatin-reactive patient, whose initial reaction was a maculopapular rash (confirmed by DPT), presented with a milder rash after first RDD, but not in future RDDs after protocol adjustments. Many oxaliplatin, paclitaxel, and gemcitabine RDD patients presented with flushing within 24 hours of RDD after a positive DPT result; this phenomenon was not observed during RDDs except for 2 patients (1 paclitaxel and 1 gemcitabine, graded as breakthrough reaction grade 1).

"Double RDDs," subcutaneous desensitizations, and 1-bag cetuximab RDDs

Eventually, more drugs became new culprit drugs as some of these 186 patients (15 of 186) suffered additional DHRs to different drugs during their RDDs. Hypersensitivity was ruled out in 60% (9 of 15) of them, but in 6 of 15 of these patients, hypersensitivity was confirmed too for that new culprit drug. Thus, 6 patients were diagnosed with hypersensitivity to 2 different drugs that they were receiving more or less simultaneously. Three oxaliplatin RDD patients (negative ST result and negative DPT result to leucovorin before starting RDDs with oxaliplatin) needed adding simultaneous leucovorin RDD after suffering a reaction during an oxaliplatin RDD (leucovorin is administered concomitantly) and confirming positive leucovorin DPT result. Two patients reacting to paclitaxel needed adding concomitant carboplatin RDD, after a reaction during carboplatin administration (administered shortly after paclitaxel RDD)

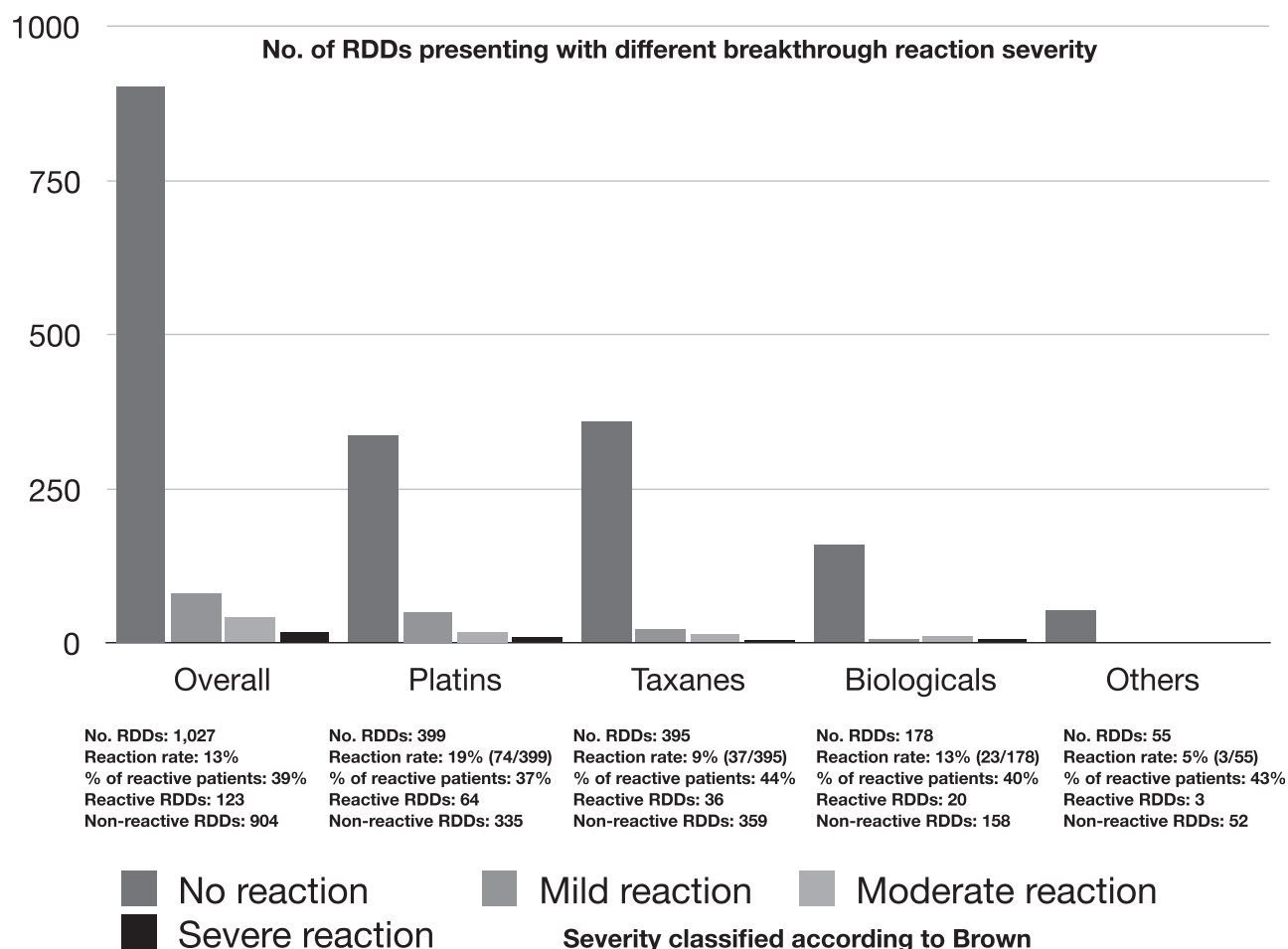


FIGURE 2. Breakthrough reactions during 1027 RDDs performed over a 7-year period at the RCUH. *RCUH*, ramon y cajal university hospital; *RDD*, rapid drug desensitization; *No*, number.

and confirming positive carboplatin ST result. One docetaxel RDD patient also needed adding concomitant cyclophosphamide RDD after suffering a reaction (confirmed with DPT). Because RDD is an antigen-specific procedure, these 6 patients thus needed a “double RDD” (a different RDD for each of both drugs) to receive both concomitant/simultaneous culprit drugs by means of RDD. To avoid confusion, patients in this study with a double RDD were categorized only on the basis of the first culprit drug causing the referral DHR.

Interestingly, 6 patients treated with subcutaneous biologicals (3 of 6 adalimumab, 1 of 6 certolizumab, 1 of 6 anakinra, 1 of 6 bortezomib) needed desensitization. However, these patients were in need of subcutaneous desensitization; therefore, they were not included in this study as candidate patients for intravenous RDD.

Ten cetuximab-reactive patients were referred. All patients had negative ST result. We excluded hypersensitivity (negative DPT result) in 4 patients. Candidates for RDD: 4 patients showed a positive DPT result, and 2 patients were classified as high-risk patients. We performed 77 one-bag RDDs to cetuximab in 6 patients over the study period. All patients received their desired doses. Two patients (33%) showed a moderate breakthrough reaction during their first RDDs. After protocol adjustments,

they tolerated their second RDDs uneventfully. No more breakthrough reactions were observed.

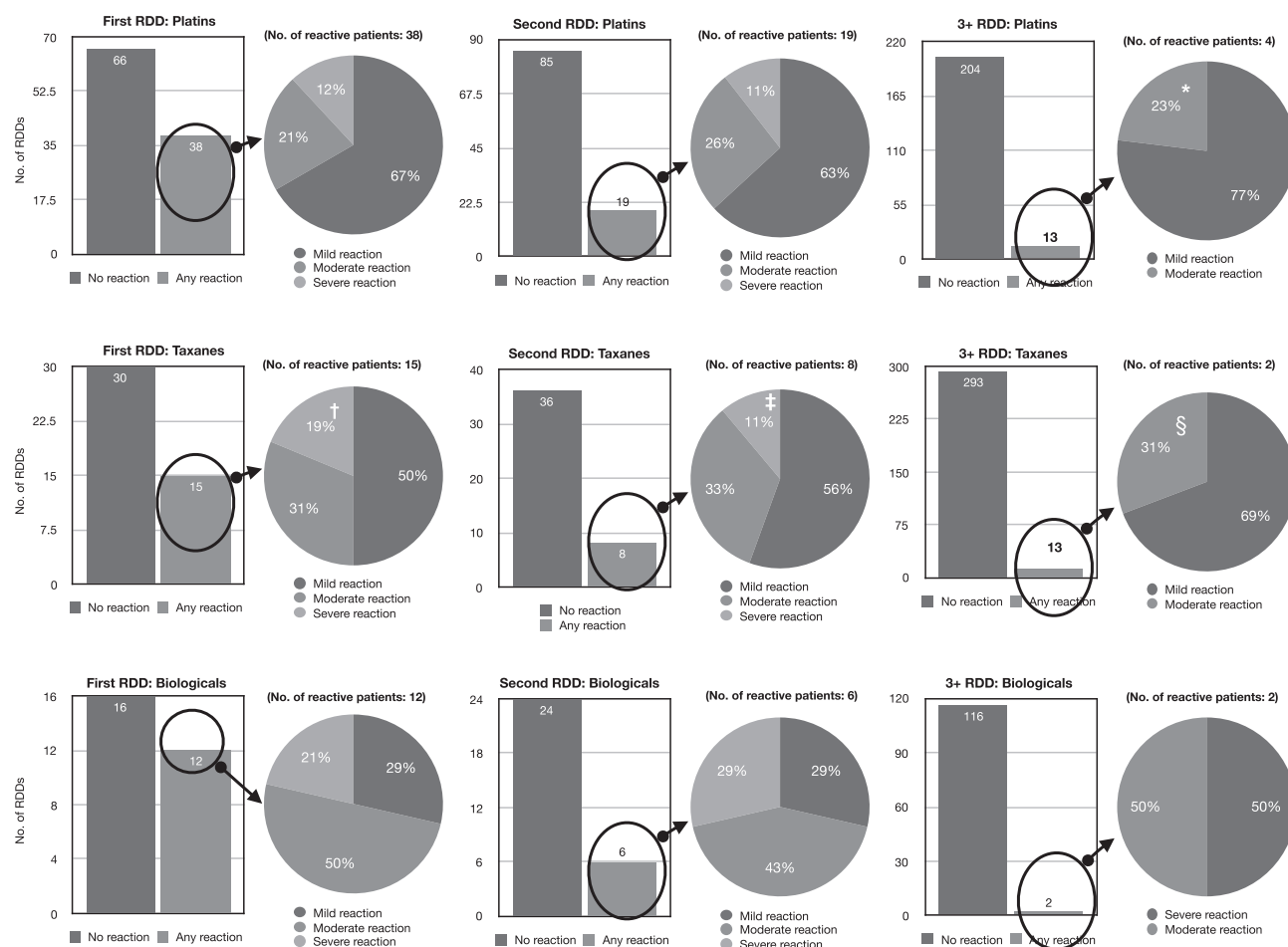
Predictors of a hypersensitivity diagnosis (see Table III)

Atopy and severity of initial reaction were not found to be predictors of a hypersensitivity diagnosis.

Taxanes: Nonimmediate reactions were more likely to have a negative hypersensitivity diagnosis (after negative DPT result) and to continue with regular administrations. Any cardiovascular symptoms and desaturation were good predictors of inconclusive diagnosis in taxane-reactive patients, because patients suffering these severe symptoms are less likely to be rechallenged.^{5,7,37}

Platins: After the multivariate analysis, we found that the most significant variables in the univariate analysis were driven by 1 variable alone. “Previous reactions” is the strongest predictor of a positive hypersensitivity diagnosis. These reactions are generally unnoticed/overlooked mild reactions during previous administrations of the same culprit drug, and they are often considered unimportant, or remain unreported for fear of treatment suspension.⁵

Interestingly, total IgE was identified as a predictor of a positive hypersensitivity diagnosis for platins.



*One mild reaction in patient forgetting premedication intake (ASA and montelukast) and one mild reaction during transition to less bags.

†One same patient accounted for two severe reactions during the same RDD

‡This severe reaction happened on a previously nonreactive high-risk patient being transitioned to 3-bag RDD

§Two of the moderate reactions happened in patients forgetting premedication intake (ASA and montelukast) and one during transition to less bags.

FIGURE 2. (Continued).

Predictors of breakthrough reactions during RDD and prevention measures

Consistent with previous data,³⁷ atopy was a factor that increased the risk of suffering breakthrough reactions during RDD. Nevertheless, the main good predictor for breakthrough reactions was positive SPT result. Patients with positive SPT tend to encompass an important percentage of breakthrough reactions and eventually may need additional measures to improve their troublesome RDD tolerance. Although patients with positive SPT results were more reactive regardless of the culprit drug, most patients with positive SPT results were oxaliplatin-reactive.

DISCUSSION

This is the first RDD study to include DPT as the diagnostic criterion standard, with data from a large cohort (more than 500 patients) consulted for DHRs to antineoplastics and biologicals in a single hospital. In this study, we report the largest series of RDDs (1027 procedures) using the RCUH protocol, and the largest series of 1-bag RDDs to cetuximab (77 procedures).

This is the largest reported series of DPTs to antineoplastic and biological agents: 341 DPTs were performed, and results for 229 were negative (67%). We found that DPTs helped exclude hypersensitivity in 44% (229 of 515) of referred patients. DPT is a risky technique and should be performed only by experts in adequate settings.⁵ However, it is a proven invaluable diagnostic criterion standard with a key role in the optimal assessment of these patients, namely, confirming or ruling out hypersensitivity, confirming a true diagnosis when 2 or more drugs are involved, and validating diagnostic tools (Table VI).⁵

Given the characteristics of our population, this is the largest reported series of oxaliplatin RDDs (347 procedures in 85 patients), selected from the largest reported cohort of oxaliplatin-reactive patients (188 assessed patients).

Severity alone or atopy persistently shows no association to the final diagnosis in our population.^{5,7} Other studies^{4,14,28,37-40} prioritize the severity of the initial reaction as a key factor or find higher prevalences of atopy and drug allergy in reactive patients. This may be due to differences in populations or differences in data collection (self-reported vs confirmed), or in the diagnostic criterion standard (eg, avoidance of DPT in diagnostic

TABLE VI. Outcomes of 341 DPTs with antineoplastic and biological agents in 515 patients referred during a 7-y period to our Desensitization Program

Results from all referred patients in 7 y (N = 515)				
DPT Result, n of total patients (%)	Taxanes (N = 135), n of N (%)	Platins (N = 188), n of N (%)	Biologicals (N = 95), n of N (%)	Other (N = 97), n of N (%)
Negative DPT result 229 of 515 (45)	70 of 135 (52)	43 of 188 (23)	47 of 95 (49)	69 of 97 (71)
Positive DPT result 112 of 515 (22)	32 of 135 (24)	50 of 188 (27)	13 of 95 (14)	17 of 97 (18)
DPT Not undergone 174 of 515 (34)	33 of 135 (24)	95 of 188 (51)	35 of 95 (37)	11 of 97 (12)
Results from the patients undergoing DPT (N = 341)				
DPT Result, n of total patients (%)	Taxanes (N = 102), n of N (%)	Platins (N = 93), n of N (%)	Biologicals (n = 60), n of N (%)	Other (n = 86), n of N (%)
Negative DPT result 229 of 341 (67%)	70 of 102 (69)	43 of 93 (46)	47 of 60 (78)	69 of 86 (80)
Positive DPT result 112 of 341 (33%)	32 of 102 (31)	50 of 93 (54)	13 of 60 (22)	17 of 86 (20)
Safety results from the patients with a positive DPT result with chemotherapy (N = 112)				
Severity of DPT DHR	Taxanes (N = 32), n of N (%)	Platins (N = 50), n of N (%)	Biologicals (n = 13), n of N (%)	Other (n = 17), n of N (%)
Brown classification, n of total patients (%)				
Grade 1 48 of 112 (43)	11 of 32 (34)	27 of 50 (54)	5 of 13 (38)	5 of 17 (29)
Grade 2 47 of 112 (42)	14 of 32 (44)	16 of 50 (32)	7 of 13 (54)	10 of 17 (59)
Grade 3 17 of 112 (15)	7 of 32 (22)	7 of 50 (14)	1 of 13 (8)	2 of 17 (12)
RCUH classification, n of total patients (%)				
Grade I 44 of 112 (39)	11 of 32 (34)	23 of 50 (46)	5 of 13 (39)	5 of 17 (29)
Grade II 38 of 112 (34)	11 of 32 (34)	14 of 50 (28)	6 of 13 (46)	7 of 17 (41)
Grade III 26 of 112 (23)	8 of 32 (25)	12 of 50 (24)	2 of 13 (15)	4 of 17 (24)
Grade IV 4 of 112 (4)	2 of 32 (6)	1 of 50 (2)	0 of 13 (0)	1 of 17 (6)

protocols may lead to false-positive diagnosis of hypersensitivity). Moreover, many other factors unrelated to the final diagnosis may be influencing the severity of initial reactions, for example, suboptimal and/or delayed treatment of reactions in oncology infusion centers, or other entities that may present with similar symptoms to anaphylaxis.^{41,42}

Effectivity and safety of RDD in our population

During a 7-year period, a total of 1027 RDDs to several antineoplastic and biological agents were performed using the standard RCUH 10-step protocol in 186 patients. All patients except for 1 paclitaxel-reactive patient (who revoked her consent to finish the procedure) could receive their target dose.

No breakthrough reactions were observed in 88% (904 of 1027) of RDDs, and most reactions were mild (58%; 79 of 137). No deaths were reported.

These data confirm that, in the hands of a desensitization program, the RCUH/RDD protocol is an effective and safe therapeutic tool for drug-hypersensitive patients.

It must be noted that our population showed similar data to other groups^{4,14,35,37-39} regarding initial reaction severity. Moreover, despite our higher initial dose for RDD and our higher infusion rates, these results show no significant increase in the number or severity of breakthrough reactions when compared with results reported by other groups.^{4,14,35,37-39}

In addition, the reported data show that the 1-bag protocol for cetuximab was effective and safe in our population. Interestingly, our RCUH/RDD protocol (and not the 1-bag protocol published by Hong et al³⁵) has been used successfully by another group for 10 procedures in 1 confirmed cetuximab-allergic patient (positive ST

result and *in vitro* tests) who showed a clear decrease in alpha-gal-specific IgE after completing these 10 RDDs.⁴³

Reactive-patient phenotypes and prevention measures

We can conclude from our data that most procedures are uneventful. The overall number of only 18 severe RDD breakthrough reactions over a 7-year period after 1027 procedures may seem reassuring; however, a total of 137 breakthrough reactions were observed in 73 patients during 123 RDDs (some patients suffered breakthrough reactions in more than 1 RDD, and some patients suffered more than 1 breakthrough reaction during one RDD). Within these reactive patients we have identified several phenotypic patterns that might need specific management:

- “First RDD”: Most RDDs were achieved with no breakthrough reactions, but approximately 39% of the desensitized patients (73 of 186), regardless of the culprit drug, suffered a breakthrough reaction during their first desensitization, and most moderate or severe breakthrough reactions occurred during the first RDD. We consequently consider the first RDD an especially high-risk procedure in need of adequate intensive surveillance installations. The second RDD shows a much lower breakthrough-reaction prevalence of 12% (22 of 185). Furthermore, once the patient achieves an RDD with no breakthrough reactions either on first attempt or after protocol adjustments (rarely after the third procedure), it is uncommon to observe new breakthrough reactions. Therefore, these patients may be transferred to lower risk areas. However, none of our RDD patients is at a zero risk of

presenting with severe DHRs, and they should all be handled in dedicated areas with specific resources, adequate surveillance, trained personnel, and the adequate supervision of expert allergists.

- B. "Breakthrough reactions after several uneventful RDDs": Some factors are repeatedly involved in these patients, and so we can identify subcategories that need different management: inadequate domiciliary premedication intake, new-onset hypersensitivity to concomitant drugs, and patients transitioning to a shorter RDD protocol (Figure 2).
- C. "Positive converters" is an especially relevant phenotypic pattern in platins, establishing the need for planning tailored follow-ups and screening ST.^{5,44,45}
- D. "Fever/chills": These atypical symptoms might be the prelude of anaphylaxis, and will benefit from excluding infectious causes, from allergy workup and, during RDDs, from premedication with nonsteroidal anti-inflammatory drugs.^{5,8}
- E. "Concomitant drugs": Patients in which at least 2 drugs might be involved in the initial reaction. DPT is an essential technique to reach a confirmatory diagnosis in patients with this phenotypic pattern. In case of proven hypersensitivity to both drugs, these patients might need "double RDD." In this study and in previous studies we have identified the most common categories: "leucovorin/oxaliplatin," "leucovorin/irinotecan," "carboplatin/paclitaxel," "cyclophosphamide/mesna," "cisplatin/manitol," "cyclophosphamide/docetaxel."^{5,6}
- F. "Positive SPT phenotypic pattern": As explained above, risk of RDD breakthrough reactions.

We can state that RDD is not only a protocol for drug administration but it is a complex and multidisciplinary system in which error prevention is key for success. There are additional safety issues that must be taken care of by expert personnel. Spillages are always a possibility, and adequate measures must be ready in our allergy installations.⁴⁶ Implementing measures like double-checking for every step, pumps with automatic multistep infusion options,⁷ intensive education/collaboration with nurse teams,⁴⁷ and further improvements in local RDD protocols such as making use of only 1 bag whenever possible^{35,48} may help avoiding this type of human error, and optimizing management.²¹⁻²³

Study limitations

There are some limitations to this study, namely, being a single-center study, the broad spectrum of drugs studied, and the rather heterogeneous study groups labeled "biologicals" and "other drugs." Future similarly large and well-designed studies (including DPT in the diagnostic protocol, given the previously explained reasons) in different populations might help to add more knowledge to this field.

CONCLUSIONS

The data from this large RDD study (more than 1000 procedures) in which DPT was the diagnostic criterion standard helped us identify key points toward optimal management of antineoplastics and biologicals hypersensitivity by

1. Detecting that even if most RDDs are uneventful, we must focus on the group of reactive patients who encompass most breakthrough reactions, including the most severe ones.

2. Identifying predictors of hypersensitivity, which may lead to future primary prevention measures.
3. Differentiating the optimal location for different procedures according to risk of breakthrough reaction.
4. Finding significant predictors of breakthrough reactions in need of special surveillance.
5. Identifying different patient phenotypic patterns in need of tailored management.
6. Validating our diagnostic/therapeutic and classificational approach (in this study 82% of patients could directly benefit from the assessment and go on with their treatments, either after excluding hypersensitivity with negative DPT results, or by means of RDD).

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