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Rapid desensitization to antineoplastic drugs in an outpatient immunoallergy clinic

Outcomes and risk factors

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ABSTRACT

Background: Hypersensitivity reactions to antineoplastic agents may lead to discontinuation of first-line treatments. Rapid drug desensitization (RDD) allows for a safe reintroduction in patients who are allergic to them.

Objective: To evaluate the safety and efficacy of the Brigham and Women's Hospital's 12-step RDD in a Portuguese patient population with cancer and to identify markers associated with breakthrough reactions (BTRs) to platins.

Methods: We conducted a retrospective review of desensitizations undertaken at the Immunoallergy Day-Care Unit of the Santa Maria Hospital in Lisbon, Portugal, from July 2008 to July 2019. Adult patients with cancer and with immediate hypersensitivity reactions were included. Skin testing was performed to platins, trastuzumab, and cetuximab. The 12-step protocol was used for most patients, and a shorter protocol was used in 9 patients who were taxane-reactive to resume regular infusions.

Results: A total of 1471 RDDs were performed in 272 patients to 136 platins, 124 taxanes, 13 monoclonal antibodies, and 10 other drugs. Skin test results were positive in 127 of patients who were platin-reactive (95.3%) and negative in patients who were cetuximab- and trastuzumab-reactive. There were 141 BTRs during RDD (9.6% of infusions), 79.4% induced by platins with the majority having mild reactions (68.8%). There were 8 patients who were paclitaxel-reactive, and who completed a shorter protocol and resumed regular infusions successfully. Multiple platin infusions (cutoff: ≥ 10) and total immunoglobulin E greater than or equal to 100 U/mL were identified as independent risk factors for BTRs in patients who were platin-reactive.

Conclusion: This large single-center study confirmed the safety and efficacy of the 12-step RDD protocol in a diverse cancer population, providing evidence of its universal applications. Total immunoglobulin E is a potentially useful biomarker to identify high-risk patients who are platin-reactive.

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Introduction

Platins and taxanes are chemotherapeutic agents most commonly implicated in hypersensitivity reactions (HSRs) in patients with cancer^{1–4}; although, in the past few decades, emergent monoclonal antibodies have led to an increase in HSRs to these

agents.^{1,2,5,6} Hypersensitivity reactions can be immunoglobulin E (IgE) and non-IgE-mediated and can lead to anaphylaxis. An IgE-mediated response has been implicated as the main mechanism for immediate reactions to platins, supported by the timing of HSRs (requiring multiple exposures before sensitization), skin test positivity,^{7–15} and, more recently, the detection of platin-specific IgEs.^{7,16–18} Most immediate HSRs to taxanes occur during the first or second infusions and have a rapid onset after starting the infusion, with the underlying mechanism not yet completely understood.^{7,19–21} Hypersensitivity reactions to monoclonal antibodies also usually occur during the first or second infusions, and their clinical presentation can vary from mild pruritus to severe

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anaphylaxis; a cytokine release syndrome presenting with fever and chills has also been associated with these agents.^{1,2,5,6}

Hypersensitivity reactions may lead to discontinuation of first-line treatments, jeopardizing the quality of life and patients' survival. When no equally effective alternative therapies are available, rapid drug desensitization (RDD) allows an effective and safer reintroduction of these drugs, even after severe anaphylaxis. It must be noted that RDD is a high-risk procedure, and safe protocols for desensitization include a 12-step protocol, based on an in vitro model of mast cell IgE-mediated antigen desensitization,²² which was adapted to human protocols, with the first series published 15 years ago.²³ In addition, RDD has allowed hundreds of patients to receive their planned treatments.^{5,8,20} Sloane et al² found that RDD does not increase health costs compared with standard treatment and does not alter the drug efficacy. In this study, we aimed to evaluate the efficacy and safety of the 12-step RDD protocol developed at the Brigham and Women's Hospital, Boston, in a diverse Portuguese cancer population. A total of 11 years of experience with RDD in an outpatient setting were presented. In addition, we wanted to identify markers associated with the increased risk for breakthrough reactions (BTRs) to platins during RDD, because previous studies found that most BTRs during RDD were induced by platins.^{2,4}

Methods

A retrospective review of the clinical records of patients with cancer who were desensitized at the Immunoallergy Day-Care Unit of the Immunoallergy Department of Hospital Santa Maria-Centro Hospitalar Universitário Lisboa Norte (HSM-CHULN), between July 2008 and July 2019 was undertaken. This study was approved by the Hospital Ethics Committee.

Clinical information concerning patient characterization was collected during the initial visit to the department. Age (all >18 years old), sex, atopy history, cancer type, number of chemotherapy infusions before HSRs, and characterization of the initial HSRs were registered. Only immediate reactions (<24 hours) were included. Patients with delayed reactions (>24 hours), exfoliative diseases, or drug reactions with eosinophilia and systemic symptoms were excluded.

The World Allergy Organization definition of atopy was used for the analysis,²⁴ defined as the personal tendency to become sensitized and produce IgE antibodies in response to ordinary exposures to an allergen (inhaled allergens or foods), leading to allergic diseases. Hypersensitivity to other drugs was also investigated.

Initial HSRs were classified according to Brown's classification,²⁵ which are as follows: (1) mild or grade 1 when there was only cutaneous to subcutaneous involvement; moderate or grade 2 when diaphoresis, vomiting, presyncope, dyspnea, stridor, wheezing, tightness in back, chest, or throat, nausea, and abdominal pain were present; and severe or grade 3 when hypoxia, asphyxia, hypotension or neurologic compromise was observed. Fever and chills, and frequent symptoms of HSRs to monoclonal antibodies and oxaliplatin (which were not included in the Brown's classification system but considered by the National Cancer Institute Common Terminology Criteria for Adverse Events²⁶) were also valued and classified as moderate if there were chills or body temperature more than 38°C, and mild if the temperature was less than 38°C.

Skin testing for platins was performed. Test workup started with a skin prick test (SPT), with the undiluted drug, as follows: for 10 mg/mL carboplatin, 5 mg/mL oxaliplatin, and 1 mg/mL cisplatin. After a negative SPT, intradermal testing started with a 100-fold dilution of the abovementioned concentrations for carboplatin and oxaliplatin to minimize the risk of large local, or even systemic, reactions, and a 10-fold dilution for cisplatin, up to 10 mg/mL,

5 mg/mL, and 1 mg/mL concentrations, respectively (eTable 1).^{7,8,12,17,27} For trastuzumab, 21 mg/mL was used for SPT,^{5,6} for cetuximab, 2 mg/mL.⁶ Subsequent intradermal testing was performed up to a 10-fold dilution. Positive (histamine 10 mg/mL) and negative (saline) controls were used. A positive skin test result was defined as a mean wheal diameter of minimum 3 mm greater than the negative control.

After the initial clinical assessment and risk stratification, RDD was recommended. All patients signed an informed consent approved by the Hospital Ethics Committee, which was integrated into the medical records that indicated the potential benefits and risks of rapid desensitization including anaphylaxis and death. The initial risk assessment included the identification of the class of drugs inducing the HSRs (platin vs nonplatin drugs), the severity of the initial reaction, and comorbidities. The desensitization protocol used was based on the Brigham and Women's Hospital's 3-bag 12-step desensitization protocol.⁸ Briefly, 3 solutions with different concentrations (A [X/100], B [X/10], and C [X], X being the nondiluted drug concentration) were infused for 6 hours in 12 consecutive steps at increasing rates and concentrations (doubling doses) every 15 minutes until the final rate of 80 cc/h was reached. For a few severe initial HSRs, a 4-bag 16-step protocol was recommended, in which the first solution was diluted at 1:1000. Premedication with an H₁- (clemastine 2 mg) and H₂- antihistamines (ranitidine 50 mg) were administered before the procedures; although, this was already included in most of the routine oncology protocols (ie, taxanes, rituximab, and doxorubicin) given that it has been found to decrease the risk of BTRs, especially to paclitaxel.²⁸ Corticosteroids were not included as regular premedication, except dexamethasone (8–10 mg), which is usually prescribed by the oncology team for antiemetic purposes in most protocols (including platins), or hydrocortisone (100 mg) for rituximab. A mild sedative (lorazepam 1 mg) was added to the premedication protocol, unless contraindicated, for anxiety.

During desensitizations, BTRs were classified for frequency and severity (Brown's classification grades 1–3) and treated according to the global emergency treatment protocol posted in the day-care unit. Epinephrine was administered in cases when hypotension, throat tightness, or neurologic impairment was observed. After patient stabilization, the assessment plan for the next desensitization was prepared. Adaptations to the initial protocol, such as adjustment of premedication before the step at which time the patient had a reaction (clemastine 2 mg and or methylprednisolone 1 mg/kg), adding an intermediate step, lengthening the final steps, or switching to the 16-step protocol, were occasionally required. Delayed reactions were recorded. In our cohort, patients who experienced severe initial HSRs to platins received a dose of additional premedication with montelukast 10 mg and acetylsalicylic acid 500 mg for 2 days before the desensitization procedures, unless otherwise contraindicated (ie, dyspeptic symptoms, previous aspirin hypersensitivity, or hematologic disorders), as suggested by Breslow et al.²⁹ Since the mid-2017, for patients with mild or moderate initial paclitaxel HSRs undergoing weekly desensitizations, the protocol was simplified in the consecutive weeks (sequential 12, 8, and 4-step RDD followed by drug challenge), as previously suggested by other authors.^{30,31} If tolerated, patients would resume regular infusions. The serum total tryptase was not routinely measured. When elevated after BTRs (cutoff: 11.4 µg/L), a second quantification at a remote time was also obtained. In addition, a substantial elevation in tryptase was defined based on the following equation: baseline tryptase multiplied by 1.2 plus 2 µg/L.³²

After 2011, an additional blood sample was collected from patients before the first desensitization procedure to quantify total IgE.

In the subgroup of patients who were platin-reactive, several markers potentially associated with an increased risk for BTRs were investigated. Variables analyzed were sex, age, the severity of the initial reaction, number of previous infusions (cutoff: 10 infusions),

Table 1

Characterization of the Patients Who Underwent Desensitization at the HSM-CHULN Between July 2008 and July 2019

Number of patients; number of desensitizations	Agent	Sex		Median age	Type of cancer	n	Number of patients; number of desensitizations
		Female	Male				
Platins (n = 136; 689)	Oxaliplatin	44 (55%)	36 (45%)	57 (27-77)	Colorectal	72	80; 402
					Pancreatic	4	
					Gastric	2	
					Testicular	1	
					Lung	1	
	Carboplatin	48 (98%)	1 (2%)	60 (29-76)	Ovarian	36	49; 258
					Endometrium	5	
					Breast	4	
					Others	4	
	Cisplatin	6 (86%)	1 (14%)	50 (27-71)	Breast	3	7; 29
					Uterine cervix	2	
Taxanes (n = 124; 604)	Docetaxel	52 (88%)	7 (12%)	51 (20-83)	Others	2	59; 185
					Breast	51	
					Prostate	5	
					Others	3	
					Breast	36	
	Paclitaxel	61 (100%)	0	52 (25-78)	Ovarian	18	61; 408
					Endometrium	5	
					Others	2	
					Prostate	4	
					Lymphoproliferative disorders	6	
Monoclonal antibodies (n = 13; 148)	Cabazitaxel	0	4 (100%)	68.5 (66-83)	Colorectal	3	3; 40
	Rituximab	1 (17%)	5 (83%)	60 (31-76)	Breast cancer	4	4; 75
	Cetuximab	1 (33.3%)	2 (66.7%)		Desmoid tumor	3	10; 30
	Trastuzumab	4 (100%)	0		Breast	2	
Others (n = 10; 30)	Liposomal Doxorubicin	4 (100%)	0	45 (25-72)	Leiomyosarcoma	2	
	Cyclophosphamide	1 (100%)	0		Lymphoproliferative disorders	3	
	Doxorubicin	1 (100%)	0				
	Gemcitabine	1 (100%)	0				
	Dacarbazine	1 (100%)	0				
	Bendamustine	1 (50%)	1 (50%)				
Total		226 (79.8%)	57 (20.2%)	54.5	283		283; 1471

Abbreviations: HSM-CHULN, Hospital Santa Maria-Centro Hospitalar Universitário Lisboa Norte; HSR, hypersensitivity reaction; N, number.

NOTE: In this table, there are a total of 283 patients instead of 272, because a patient was counted twice if they underwent RDD to separate agents. Multiple desensitizations were as follows: 1 triple (HSRs to paclitaxel and carboplatin then switched to cisplatin), and 9 double desensitizations (HSRs to carboplatin and paclitaxel [3], HSRs to paclitaxel and trastuzumab [2], and empirical desensitizations because of previous severe HSRs and desensitizations to other drugs from the same group [2 cisplatin, 1 docetaxel, and 1 cabazitaxel]).

strongly positive skin test results (positive on SPT or the first levels of the intradermal test), atopy, and high total IgE (cutoff: 100 U/mL).

Statistical Analysis

Categorical variables were presented as frequencies and percentages, and continuous variables as means and SDs, or medians and interquartile ranges for variables with skewed distributions. Normal distribution was confirmed using the Shapiro-Wilk test for skewness and kurtosis. For total IgE comparisons between patients reacting to platins and other antineoplastic drugs, the Mann-Whitney test was applied. For the analyses of the risk factors for BTRs, categorical variables were compared using Fisher exact test or the χ^2 test, as appropriate. Variables with a *P* value lower than .10 on bivariate analysis were considered candidates for multivariate analysis that was conducted through a binary logistic regression model. *P* values lower than .05 were considered statistically significant. Analyses were performed by using IBM SPSS software (version 25.0).

Results

A retrospective review of the clinical records of patients with cancer undergoing RDD was performed and found 272 patients desensitized to 283 chemotherapeutic agents (10 patients were desensitized to 2 or 3 separate agents), with a total of 1471 desensitizations. All RDDs took place at the Immunoallergy Day-Care Unit (outpatient setting).

Patient Characteristics

As given in Table 1, most patients were female (79.8%) because many patients had gynecologic and breast cancers. The median age was 54.5 (20-93) years.

Most antineoplastics were platins that accounted for 48% of the patients included (n = 136), with a higher number of oxaliplatin use (n = 80). The most prevalent diagnosis in the desensitized population was breast cancer (n = 97, 35.7%), followed by colorectal (n = 75, 27.6%) and ovarian cancer (n = 47, 17.3%). Most patients (n = 162, 94%) underwent the 3-bag 12-step RDD protocol. A total of 10 patients with anaphylactic shock as initial HSRs received a 4-bag 16-step protocol, whereas 9 patients who were paclitaxel-reactive receiving weekly paclitaxel underwent the weekly simplification of the protocol (12-step, 8-step, 4-step, and graded challenge).

Atopy

In this series, 23 patients (8.4%) had previous history of atopy (taxanes = 12, platins = 9, monoclonals = 2). Furthermore, 9 patients had hypersensitivity to other drugs. The information regarding atopy status was not available in the notes of 38 patients.

Characteristics of the Initial Hypersensitivity Reactions

As depicted in Table 2, there were 272 patients with initial HSRs occurring at the Oncology Infusion Unit. A total of 11 patients with no previous HSRs who were referred for the evaluation of platin sensitization (6 carboplatin, 1 oxaliplatin) received positive results to skin test after 7 to 9 exposures (4 with previous negative results

Table 2
Characteristics of the Initial Hypersensitivity Reactions

Class of drug	Agent (number of patients)	Median infusion number at which patients reacted (min-max)	Classification of the initial reaction					Grade 3
			Grade 1	Grade 2		≥ 2 Organ involvement with or without skin		
			Skin only	Skin plus:				
				Respiratory	Gastrointestinal		Throat, chest, back, or pelvic pain	
Platins (127)	Oxaliplatin (79) ^a	10 (2-37)	19	22	6	3	12	17
	Carboplatin (43) ^a	9 (5-17)	5	12	4	2	5	15
	Cisplatin (5) ^a	7 (2-8)	3	2		0	0	0
Taxane (122)	Paclitaxel (61)	2 (1-5)	2	16	2	18	15	8
	Doxetaxel (58) ^b	2 (1-5)	2	16	4	19	10	7
	Cabazitaxel (3) ^b	2	0	0	0	0	1	2
	Rituximab (6)	2 (1-8)	0	1	0	1	0	4
Monoclonal antibodies (13)	Trastuzumab (4)		0	1	1	1	0	1
	Cetuximab (3)		0	1	0	0	1	1
	Liposomal Doxorubicin (4)	1 (1-2)	0	2	0	1	0	1
Other drugs (10)	Bendamustine (2)		2	0	0	0	0	0
	Doxorubicin (1)		0	0	0	1	0	0
	Cyclophosphamide (1)		1	0	0	0	0	0
	Gemcitabine (1)		1	0	0	0	0	0
	Dacarbazine (1)		0	1	0	0	0	0
	272 ^a	3	35	74	17	46	44	56
	Subtotals							
Totals				181				

Abbreviation: HSR, hypersensitivity reaction.

^aIn 11 patients desensitized to platins, there was no initial HSR, because these patients were referred to evaluate platin sensitization after 7 to 9 treatment infusions.^bTwo patients receiving taxanes (docetaxel and cabazitaxel) were switched to another taxane and were desensitized on the basis of the severity of the initial reaction to the other taxane.

became positive on re-exposure), and were then desensitized. For the platin group, the median infusion number at which patients had a reaction was high (7 for cisplatin, 9 for carboplatin, and 10 for oxaliplatin). Most patients with HSRs to taxanes, monoclonal antibodies, and other drugs had a reaction during the first or second infusions (n = 121, 82.3%).

Most initial HSRs were moderate to severe (n = 237, 87%), with only 13% (n = 35) mild. Skin involvement was present in most patients (n = 201, 74%), even in grade 3 HSRs (n = 29, 51.8%).

Most HSRs to monoclonal antibodies (n = 7) and some oxaliplatin (n = 4) presented with fever and chills. Out of 6 HSRs, 4 reactions to rituximab were severe and occurred during the second infusion. A high percentage of moderate and severe HSRs to taxanes included neuromuscular symptoms, particularly, thoracic or back pain (n = 69, 55.6%), and some had no skin involvement (n = 21).

Results of the Skin Testing

Skin tests were conducted for platins and 2 monoclonal antibodies (trastuzumab and cetuximab). As depicted in eTable 1, for most patients who were platinum-reactive, a skin test was done (n = 127, 93.3%). Most patients had a positive test result for intradermal testing, and 8.5% of carboplatin and 10.5% of oxaliplatin patients had positive results for SPT. Patients with 4% of oxaliplatin and 4.5% of carboplatin had negative results in skin testing and were desensitized on the basis of the severity of the initial reaction (all grade 2 HSRs) because the negative predictive value of platins skin test is unknown.

Skin tests to trastuzumab and cetuximab were uniformly negative. Patients receiving taxanes, monoclonal antibodies such as rituximab, and other drugs did not undergo a skin test. The use of high doses of systemic steroids (lymphoproliferative disorders) and antihistamines, limitations in timing (such as weekly trastuzumab infusions), cutaneous toxicity (eg, doxorubicin), or other nonclinical reasons (such as patients' preferences) limited skin testing.

Breakthrough Reactions During Desensitization

As depicted in Table 3, 141 BTRs occurred (corresponding to 9.6% of the desensitization procedures) in 80 patients (29.4% of all patients), with 17 of them being recurrent (maximum 4 BTRs per patient). Most of the recurrent BTRs were induced by platins (n = 13, 76.4%). A vast majority were grade 1 (n = 97, 68.8%), whereas 36 were grade 2 (25.5%) and 8 were grade 3 HSRs (5.7%). In general, most of the reactions were milder than the index reaction (although 5 patients had a moderate BTR after a mild index HSR).

Platins were responsible for the majority of the BTRs (n = 112, 79.4%), with the more severe ones being the culprit in 6 of 8 severe reactions (75%) and 21 of 36 moderate HSRs (58.3%).

As depicted in Figure 1A, most BTRs occurred during the first RDD (n = 58, 41%), including 5 of 8 severe HSRs (62.5%); 45 of 53 BTRs that occurred after the second desensitization (85%) were induced by platins.

There were no BTRs during the infusion of bag 1 and the majority occurred during the infusion of the last bag of the protocol (n = 111, 78.7%) (Fig 1B). Most BTRs occurred at the last step of the protocol (n = 97, 69%), whether on the 12th step of the 12-step protocol or the 16th of the 16-step protocol.

Once a BTR occurred, the infusion was stopped, treatment was provided to address the symptoms and the infusion was resumed once symptoms improved. Depending on the step and severity of the BTR, different adaptations were proposed for subsequent RDD. A total of 7 patients were switched to a 4-bag protocol because of BTRs occurring before bag 3. Because many patients had a reaction at step 12, an intermediate step, 11B at 60 cc/h, was added, and steps 10 and 11

Table 3
Breakthrough Hypersensitivity Reactions During Desensitization

Class of drug	Agent (number of reactions and patients)	Breakthrough reactions during desensitization					
		Grade 1	Grade 2				Grade 3
		Skin only	Skin plus:			≥ 2 Organ involvement with or without skin	
			Respiratory	Gastrointestinal	Chest, back, or pelvic pain		
Platins 112 BTRs out of 689 infusions (16.3%)	Carboplatin (54 BTRs in 24 patients)	40	3	0	8	3	3
	Cisplatin (1)	44	3	2	1	1	3
	Paclitaxel (15 BTRs in 14 patients)	1	0	0	0	0	0
Taxanes 23 BTRs of 604 infusions (4%)	Doxetaxel (8 BTRs in 7 patients)	3	3	0	6	1	2
	Rituximab (3 BTR in 2 patients)	5	0	0	3	0	0
Monoclonal antibodies 3 BTRs of 148 infusions (2%)	Bendamustine (3 BTRs in 2 patients)	2	0	0	0	1	0
Other drugs 3 BTRs of 30 infusions (10%)	Carboplatin (54 BTRs in 24 patients)	2	0	1	0	0	0
Subtotals	141	97	9	3	18	6	8
Totals	breakthrough BTRs (9.6%) in 80 patients (29.4%)		36				

Abbreviations: BTR, breakthrough reaction; HSR, hypersensitivity reaction.

were lengthened from 15 to 30 minutes. In addition, methylprednisolone (40–80 mg) and clemastine 2 mg were recommended before the step at which the patient reacted. A combination of these management strategies was frequently used in recurrent BTRs. When patients were not receiving aspirin and montelukast, these drugs were added to the pre-medication plan.

Intramuscular epinephrine 0.5 cc (1 mg/mL) was administered in 11 patients (8 had severe BTRs and 3 patients had grade 2 BTRs). One patient with a severe BTR to carboplatin required 2 epinephrine injections because of biphasic anaphylaxis; thus, the desensitization was discontinued. This was the only patient who did not accomplish the target chemotherapy dose.

Regarding patients undergoing paclitaxel RDD who underwent the simplification of the protocol (8-step, 4-step, and challenge), 8 of 9 tolerated this approach and received weekly regular infusions at the Oncology Infusion Unit. Only 1 patient had a BTR on the seventh step of the 8-step protocol (because of severe back pain) and resumed the 12-step RDD for her last planned treatment with no BTR.

There were no hospitalizations or deaths related to RDD procedures.

Biomarkers: Serum Tryptase, Total Immunoglobulin E

Although there were no tryptase measurements at the time of the initial reactions, tryptase was elevated in 2 patients (1 and 2)

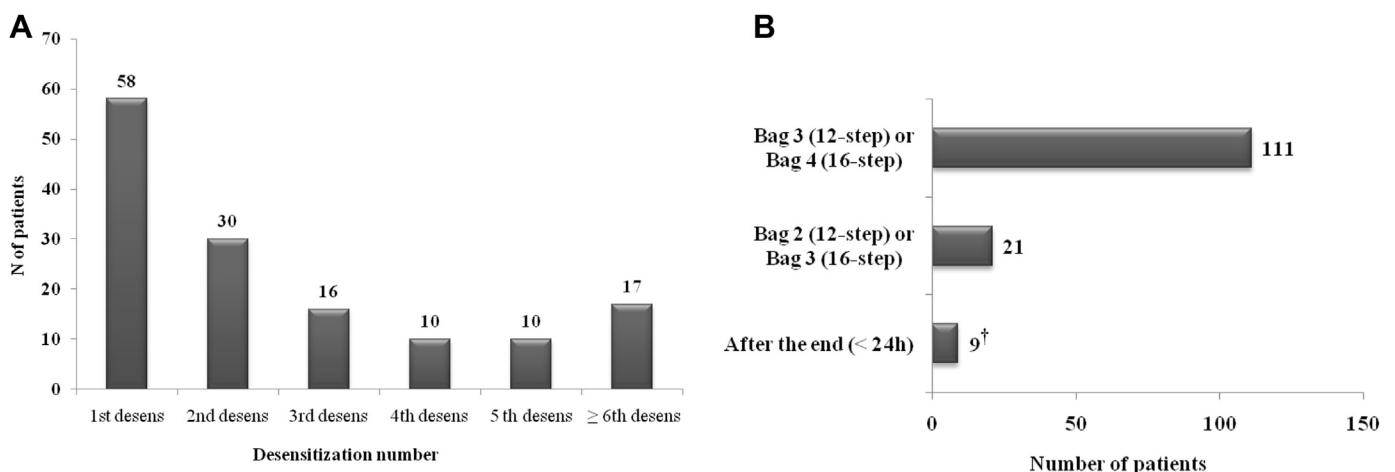


Figure 1. Desensitization number (A) and bag number (B) at which breakthrough hypersensitivity reactions occurred.

Table 4
Serum Tryptase Measurements After Breakthrough Hypersensitivity Reactions and at Baseline

Patient number	Age	Cancer	Agent	Description of breakthrough HSR	Severity of HSR	Serum tryptase (cutoff: 11.4 µg/L)	
						After breakthrough HSR	Baseline
1	56	Colorectal	Oxaliplatin	Fever, chills, rash, hypotension	3	12.1	5.6
2	62	Ovarian	Carboplatin	Rash, dyspnea with hypoxemia, and hypotension	3	17.2	3.7
3	37	Breast	Carboplatin	Rash, abdominal pain, nausea, hypotension (biphasic)	3	4.8	2.8
4	60	Colorectal	Oxaliplatin	Flushing, thoracic pain, dyspnea	2	6.0	5.6
5	48	Breast	Docetaxel	Flushing, cervical pain malaise with feeling of faintness	2	5.9	3.3
6	53	Breast	Docetaxel	Flushing and back pain	2	5.3	3.2

Abbreviation: HSR, hypersensitivity reaction.

during BTRs, and considering the tryptase equation (20% of baseline + 2 µg/L), 1 more patient with a borderline tryptase increase was identified (patient 5), as shown in Table 4.

Blood was collected from 163 patients to measure total IgE, of which 77 patients were found desensitized to platins and 86 desensitized to other antineoplastics. All samples were collected after the initial HSRs and before the first desensitization.

Total IgE was significantly higher in the platins group (median 105 U/mL [40.40–245.5]) than in the group including all other agents (median 24.25 U/mL [7.75–80.58]) ($P < .001$). The subgroup of patients who were platin-reactive was further analyzed ($n = 127$) to investigate potential risk factors for BTRs. The following 2 groups were compared: group 1 included patients experiencing minimum 1 BTR during any RDD procedure ($n = 56$), and group 2 included patients without BTRs ($n = 71$). The results for the different variables were listed in Table 5. The percentage of young patients and females did not differ significantly between groups 1 and 2. A significantly higher percentage of patients in group 1 had an

initial moderate to severe HSR (89.3% vs 70.4%; $P = .01$). The difference was not statistically significant when analyzing the patients with severe HSRs only ($n = 31$), between groups (30.3% vs 19.7%, $P = .17$). For the number of previous platin infusions, strongly positive skin test results (positive on SPT or the first levels of the intradermal test) and atopy, the difference between the 2 groups did not reach statistical significance ($P = .08$, .051, and .89 respectively).

Regarding total IgE, a significant difference between the 2 groups was found, with 73.1% of patients from group 1 vs 39.1% from group 2 having a total IgE of greater than 100 U/mL ($P = .006$).

Bivariate analysis of the potential risk factors considered was performed (Fig 2). Two of the 7 variables analyzed demonstrated a positive association with the presence of a BTR during desensitization, namely, the initial HSR grade 2 or 3 (odds ratio [OR] 3.50; $P = .01$) and total IgE greater than or equal to 100 U/mL (OR 4.22; $P = .006$).

After multivariate analysis using a binary logistic regression model, in which the variables with a P value less than or equal to .10 in the bivariate analysis were included, total IgE greater than or

Table 5
Comparison Between Groups of the Potential Risk Factors Analyzed for Breakthrough Reactions

Potential risk factors evaluated	Total		Group 1 (HSRs during PD)		Group 2 (without HSRs)		P value
Total number of patients	127		56		71		
Sex, n (%)							
Female	90	(70.9)	39	(69.6)	51	(71.8)	.94
Male	37	(29.1)	17	(30.4)	20	(28.2)	
Age range, n (%)							
<50 y	20	(15.7)	8	(14.3)	12	(16.9)	.69
≥50 y	107	(84.3)	48	(85.7)	59	(83.1)	
Severity of initial HRS, n (%)							
Moderate to severe	100	(78.7)	50	(89.3)	50	(70.4)	.01
Mild	27	(21.3)	6	(10.7)	21	(29.6)	
Previous platin infusions, ^a n (%)							
≥10 infusions	66	(52)	34	(60.7)	32	(45.1)	.08
<10 infusions	61	(48)	22	(39.3)	39	(54.9)	
Skin tests, ^b n (%)							
Strongly positive	105	(87.5)	49	(94.2)	56	(82.4)	.051
Weakly positive/negative	15	(11.8)	4	(7.2)	11	(15.5)	
Atopy, ^c n (%)							
Yes	14	(11.8)	6	(10.7)	8	(12.1)	.89
No	105	(88.2)	47	(83.9)	58	(87.9)	
Total IgE, ^{d,e} n (%)							
≥100 U/mL	37	(51.4)	19	(73.1)	18	(39.1)	.006
<100 U/mL	35	(48.6)	7	(26.9)	28	(60.9)	

Abbreviations: HSR, hypersensitivity reaction; IQR, interquartile range; PD, platin desensitization; SPT, skin prick test.

NOTE: Strongly positive skin test results: positive on SPT or the first levels of intradermal test. Weakly positive skin test results: positive on the last level of intradermal test (1:1 dilution).

^aGroup 1: median 10 (range 3–37; IQR 6); group 2: median 9 (range 2–21; IQR 6).

^bFor skin tests, 7 missing values, 4 of them from group 1.

^cFor atopy, 8 missing values, 3 of them from group 1.

^dFor total IgE, 55 missing values, 30 of them from group 1.

^eGroup 1: median 156.5 U/mL (range 5.4–1088; IQR 391); group 2: median 57.1 U/mL (range 2.5–4734; IQR 135.3).

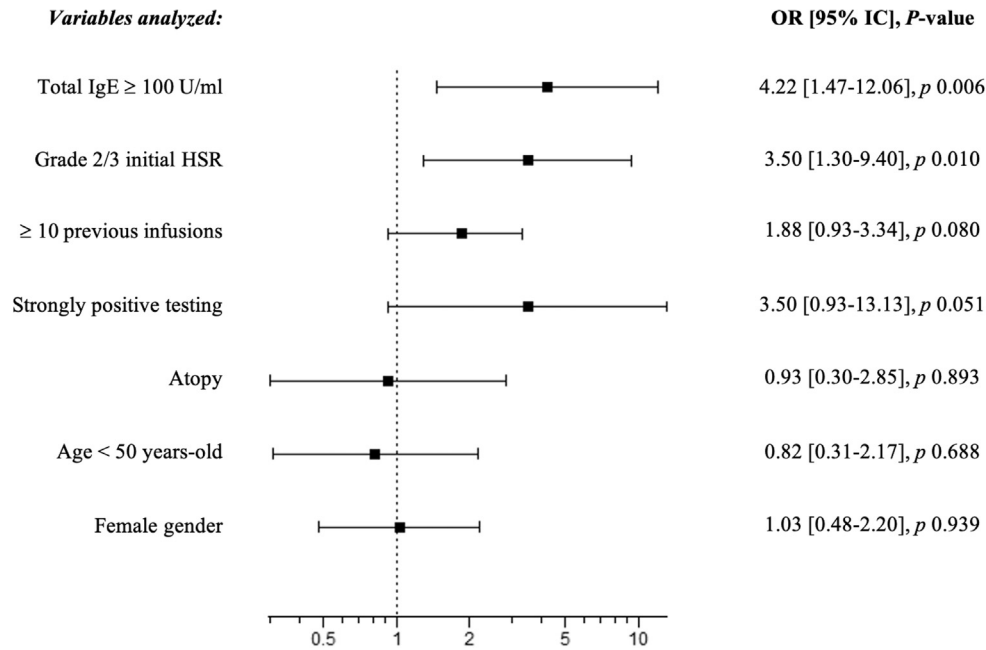


Figure 2. Forest plot representing bivariate analysis of the potential risk factors for rapid drug desensitization to platins

equal to 100 U/mL and 10 or more previous infusions showed statistical significance, with adjusted ORs of 8.24 and 4.11, respectively (Table 6). These 2 variables were, therefore, independent predictors for BTRs during desensitization. Based on our data, in every 3 patients with a total IgE greater than or equal to 100 U/mL, one would expect a breakthrough reaction (ie, the number needed to test was 3).

Discussion

We presented here the largest European series of RDD to anti-neoplastic agents performed in an outpatient setting. A total of 11 years of experience with RDD to antineoplastic agents were presented, including chemotherapeutic drugs and biological agents. Patients with cancer who have suspected HSRs were referred to our department for initial evaluation, and when indicated, desensitization was recommended. Of note, RDD was highly effective (1470 of 1471 completed), and safe, with 97% (1427 of 1471) of the RDD procedures elicited only mild (*n* = 97, 6.6%) or no (*n* = 1330, 90.4%) BTRs, and no hospitalizations or deaths occurred. Previous authors had recommended that the first RDD should take place at an intensive care unit;^{4,8} although, recently, it has been found that outpatient desensitizations were safe.^{2,33} In addition, RDDs were performed in an outpatient unit inside the hospital, proximal to the emergency department, and emergency equipment and personnel trained in advanced life support were readily available. These factors enabled safe maintenance of the RDD procedures in the Immunoallergy Day-Care Unit.

In this cohort of 272 patients, a higher number of patients were noted to have oxaliplatin allergy than carboplatin, similar to a previous study from Spain⁴ and different from a larger series in Boston.² Oxaliplatin has been found to act differently from other platins because its mechanism of action is based not only on the inhibition the transcription of DNA into RNA, but also on its direct interactions with the immune system.³⁴ In addition, oxaliplatin in vitro high immunogenicity has also been previously described,¹⁶ possibly justifying its higher sensitization profile. These geographic differences could be furthermore explained by the higher prevalence of colorectal cancer in Portugal and Spain than in the United

States.³⁵ A high percentage of patients had moderate to severe initial reactions (87%). For mild HSR to a nonplatin agent, a graded challenge was conducted at the Oncology Infusion Unit under our supervision. The results of skin testing to platins confirmed the high sensitivity of this diagnostic tool (95.3% in this cohort), and its use guided us in determining the culprit drug when different antineoplastic agents were administered in combination. In this cohort, patients who had taxane were not given a skin test. Picard et al³⁰ have validated taxanes skin testing for risk stratification, and more recently Pagani et al²¹ found that, in Europe, the sensitivity of skin testing to both paclitaxel and docetaxel was only 16.7%. In this series, most HSRs to taxanes occurred in the first or second infusions, possibly implicating the diluents cremophor and polysorbate.²⁸

There were 141 breakthrough HSRs (9.6% of all procedures), consistent with previous studies, even with a high percentage of moderate to severe initial HSRs (*n* = 237, 87%). Although most BTRs occurred in the first desensitization, we observed reactions after 6 desensitizations, the majority induced by platins (89%), indicating that IgE sensitization can increase after multiple exposures, including during desensitization. Tryptase levels were elevated in 3 reactive patients, indicating that mast cell activation occurred, and that desensitizations should be considered high-risk procedures.

Table 6

Multivariate Analysis of the Potential Risk Factors Considered for Breakthrough Reactions Through a Binary Logistic Regression Model

Potential risk factors evaluated	OR	CI (95%)	P value ^a
Total IgE ≥ 100 U/mL	8.24	2.06-30.02	.001
≥10 Previous infusions	4.11	1.17-14.52	.03
Grade 2 or 3 initial HSR	2.19	0.38-12.79	.38
Strongly positive testing	1.55	0.21-11.46	.67

Abbreviations: CI, confidence interval; HSR, hypersensitivity reaction; OR, odds ratio; SPT, skin prick test.

NOTE: Strongly positive skin test results: positive on SPT or the first levels of intradermal test.

^aAdjusted factors for binary logistic regression: severity grade of initial HSR, skin test result, previous infusions, and total IgE.

The prevalence of atopy (8.4%) was lower than that observed in previous studies (45% in a large cohort from Boston,² and 29% in a recent Spanish study⁴). Despite this low prevalence, total IgE was noted to be elevated in patients who were platin-reactive, especially among patients experiencing BTRs.

There was no significant association between BTRs and age, sex, highly positive skin test results to the culprit drug, or atopy.

The severity of the initial HSR showed a significant OR for the presence of BTRs, although not independently in this cohort. This has been described before by Sloane et al,² who reported that patients with an initial grade 3 HSRs had a 9% chance of a grade 3 BTRs during their first RDD.

In this cohort, the following 2 independent predictors for BTRs were identified: 10 or more infusion courses and high total IgE (≥ 100 U/mL). Multiple infusion courses have been previously reported as a risk factor for platin hypersensitivity^{2,9,11,25,36}; but, to the best of our knowledge, this was the first study that showed an association with increased risk for BTRs during RDD. High total IgE was the strongest independent predictor of BTRs during platin desensitization. Recently, total IgE was identified as a predictor of a positive hypersensitivity diagnosis for platins, although the timing of the blood collection was not specified.⁴ Moreover, some antineoplastics, such as alkylating agents, are known to reverse the normal suppression of allergic responses and to potentiate selective IgE production, either to general or specific antigens.³⁷ Taking all of this into account, it is yet to be determined whether the higher IgE levels in these patients are induced by the HSRs, the repeated exposure and gradual sensitization, or the platinum drug itself. Nevertheless, it should be considered as a risk factor, and, potentially, all patients with platin HSRs should have an IgE level determined to further stratify the risk of having BTRs during RDD.

This study has some limitations. Although the sample size was not calculated, we have analyzed the power of the tests used to compare the candidate variables for risk factors with BTRs during RDD and obtained a power above 80% in the tests that revealed results that are statistically significant. The analyses of the remaining variables should be interpreted with caution, because with a power lower than 80%, type II errors cannot be excluded. Moreover, this is a retrospective study, and some of the data collected were not complete. In addition to the relatively small patient sample, only patients receiving RDD after 2011 had a total IgE determination, limiting our conclusions. To extrapolate these results, multicenter studies are critical.

Despite the abovementioned limitations, this large single-center study confirms the efficacy and safety of the 12-step RDD protocol in a diverse cancer population in an outpatient setting, reinforcing its universal applicability. We provided evidence that increased levels of total IgE (≥ 100 U/mL) and a high number of platin infusions (≥ 10) were risk factors for BTRs during RDD. An elevated total IgE in patients who were platin-reactive and undergoing RDD could be a helpful marker to identify high-risk patients who were platin-reactive. This approach would consolidate the initial assessment and risk stratification, potentially imposing adjustments to each individual protocol, such as recommending a 16-step protocol and adding aspirin and montelukast to the premedication plan.

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Supplementary Data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.anai.2020.04.017>.

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Supplementary Data

eTable 1

Skin Testing Concentrations Used in Platin-Reactive Patients

Patients given a skin test	Positive on SPT, n (%)		Positive on intradermal, n (%)		Negative, n (%)
Carboplatin (47 of a total of 49)	10 mg/mL	4 (8.5)	0.1 mg/mL	1 mg/mL	10 mg/mL
			32 (68)	8 (17)	1 (2)
Oxaliplatin (76 of a total of 80)	5 mg/mL	8 (10.5)	0.05 mg/mL	0.5 mg/mL	5 mg/mL
			14 (18.5)	46 (60.5)	5 (6.5)
Cisplatin (4 of a total of 7)	1 mg/mL	0	0.1 mg/mL	1 mg/mL	1 mg/mL
			1 (25%)	2 (50%)	1 (25)
Total (127-93, 3% platin patients tested)	12 (9.5)		109 (86)		6 (4.5)

Abbreviations: n, number; SPT, skin prick test.