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Rapid drug desensitization with platin-based chemotherapy: Analysis of risk factors for breakthrough reactions

Begum Gorgulu Akin, MD[a], Merve Erkoc, MD[a], Elif Tugce Korkmaz, MD[a], Betul Ozdel Ozturk, MD[a], Sevgi Colak, MD[a], Funda Seher Ozalp Ates, MD[b] and Sevim Bavbek, MD[a]*

ABSTRACT

Background: All platin-based chemotherapeutics can cause hypersensitivity reactions (HSRs). With rapid drug desensitization (RDD), few patients experience breakthrough reactions (BTR) during desensitization. However, data about risk factors for BTRs during RDD in patients with HSRs to platins are limited. We first aimed to describe characteristics of our platin-reactive population and to validate the Brigham and Women's Hospital's (BWH's) RDD protocol in our population along with their outcomes with RDD. Our second aim was to identify the risk factors for BTRs.

Method: This was a retrospective chart review (2013–2020) of patients with symptoms of immediate HSRs to platins. Initial HSRs were classified as grade 1, 2, or 3 based on their severity. Skin prick tests (SPT)/intradermal tests (IDT) were performed with implicated platins. A 12-step protocol was used during RDD.

Results: The study comprised 65 women and seven men (mean age 57.78 $\pm$ 8.73 years). Initial HSRs to carboplatin, cisplatin, and oxaliplatin occurred in 38, 13, and 21 patients, respectively. All patients reacted at the fifth (median) recurrent infusions (min:1, max:20). The median values for carboplatin, cisplatin, and oxaliplatin were 6 (1–20), 3 (1–15), and 3 (1–11), respectively. Most initial HSRs were grade 2 (n = 40, 55.6%) and 3 (n = 27, 37.5%); only 6.9% (n = 5) were grade 1. Patients with grade 1, 2, and 3 initial HSRs had positive platin skin test results at rates of 80%, 74%, and 88%, respectively.
A total of 232 RDDs were performed in 72 patients and 98.7% of these desensitizations were completed. BTRs occurred in 56 (24.1%) (grade 1 n = 14, 25%; grade 2 n = 32, 57%; grade 3 n = 10, 18%) of these desensitizations. Breakthrough reactions were more severe in patients with positive SPTs or 1:100 or 1:10 dilutions of IDT (p = 0.014). BTR was not observed during RDD in any of the patients with positive 1:1 dilutions of IDT. Positivity on prick or 1:100 or 1:10 IDT increased the risk of BTR 5.058 times. There was no significant association between the risk of BTRs and age, drug cycle, sex, comorbidities, or atopy.

Conclusion: In our experience, 98.7% of 232 RDDs to platins were completed successfully, showing that RDD was safe and effective. Drug skin test positivity is a potential marker for identifying high-risk patients who will have BTRs during RDDs to platins.

Keywords: Breakthrough reaction, Hypersensitivity reactions, Platins, Rapid drug desensitization

[a]Division of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey
*Corresponding author. E-mail: bavbek@medicine.ankara.edu.tr

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INTRODUCTION

Platins are an option for the treatment of malignancies and are frequent causes of hypersensitivity reactions (HSRs), which generally occur within the first hour of infusion. The clinical manifestations of HSRs vary considerably from mild to severe and life-threatening anaphylaxis.[1,2] The incidence of HSRs to cisplatin was 5–20% and was 7–24% for oxaliplatin. The incidence of HSRs to carboplatin varies in different malignancies. It was reported as 8–16%, 9%, and 21–42% in gynecologic cancers, solid tumors, and low-grade gliomas, respectively.[3]

An immunoglobulin (Ig)-E–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, and, more recently, the detection of platin-specific IgEs.[4–6]

Skin prick test (SPT) and intradermal test (IDT) are performed to detect drug-specific IgE to platinum compounds. Although data are limited for the sensitivity of skin tests for cisplatin, carboplatin skin tests are positive in up to 100% of patients in cases of severe reactions with a negative predictive value ranging between 81% and 98.5% and a positive predictive value of 86% in patients with recurrent gynecologic cancer.[7,8] Skin test positivity in subjects with oxaliplatin hypersensitivity ranges from 26% to 100% with a negative predictive value ranging from 95% to 56%, depending on the population.[8]

When a patient experiences an immediate HSR to a platin, the action taken most often is to stop the implicated drug, even in responsive patients, and switch to an alternative medication that may be potentially more toxic or less effective.[9] If the culprit drug is the best medication or the only alternative for the patient, desensitization can allow the continuation of the appropriate treatment. Although many desensitization protocols have been used to date, it is recommended to use protocols that have been validated in large series of patients such as the rapid drug desensitization (RDD) protocols of Brigham and Women's Hospital (BWH), Massachusetts General Hospital, and Ramon y Cajal University Hospital.[10] We have been using the RDD protocol developed by BWH since 2013 because it neatly fits with the local characteristics of our centre.[11,12]

To date, we have performed a total of 232 RDDs to platins in 72 patients. Therefore, we first aimed to describe the characteristics of our platin-reactive population and to validate the BWH's RDD protocol in our population along with their outcomes with RDD. Our second aim was to identify the risk factors for BTRs. In the literature, the data reported about risk factors in patients with platin HSRs and BTRs are limited.[5,13] We believe that the definition of these risk factors will help physicians in taking necessary and timely precautions.

MATERIALS & METHODS

Study design

The study includes a retrospective chart review (2013–2020) of patients with symptoms of immediate HSRs to platins. We used the same study method with chemotherapeutics and biologics as in our previous trial.[11,12] This study was approved by the local Ethics Committee (approval number: İ7-416-20). After the study was approved, informed consent was obtained from all participants. The study design is summarized in Fig. 1.

Subjects

Patients who presented with symptoms of immediate-type HSRs to platins were eligible for RDD. Immediate HSRs were classified as mild (Grade 1), moderate (Grade 2), or severe (Grade 3), in accordance with Brown's grading system.[14] Signs and symptoms of HSRs were defined as cutaneous (flushing, pruritus, urticaria, angioedema), cardiovascular (chest pain, tachycardia, presyncope, syncope, and hypotension), respiratory (nasal-ocular symptoms, dyspnea, wheezing, and oxygen desaturation, throat tightness), gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), and atypical manifestations (fever/chills, back and neck pain, numbness/weakness). The HSR was considered as mild if there was only a cutaneous presentation, as moderate if findings demonstrated the involvement of the respiratory, cardiovascular and gastrointestinal tract. If hypoxia, hypotension, and decompensation of the neurologic system were present, it was considered severe. Moreover, a temperature higher than 38 °C was also classified as a moderate reaction.[14]

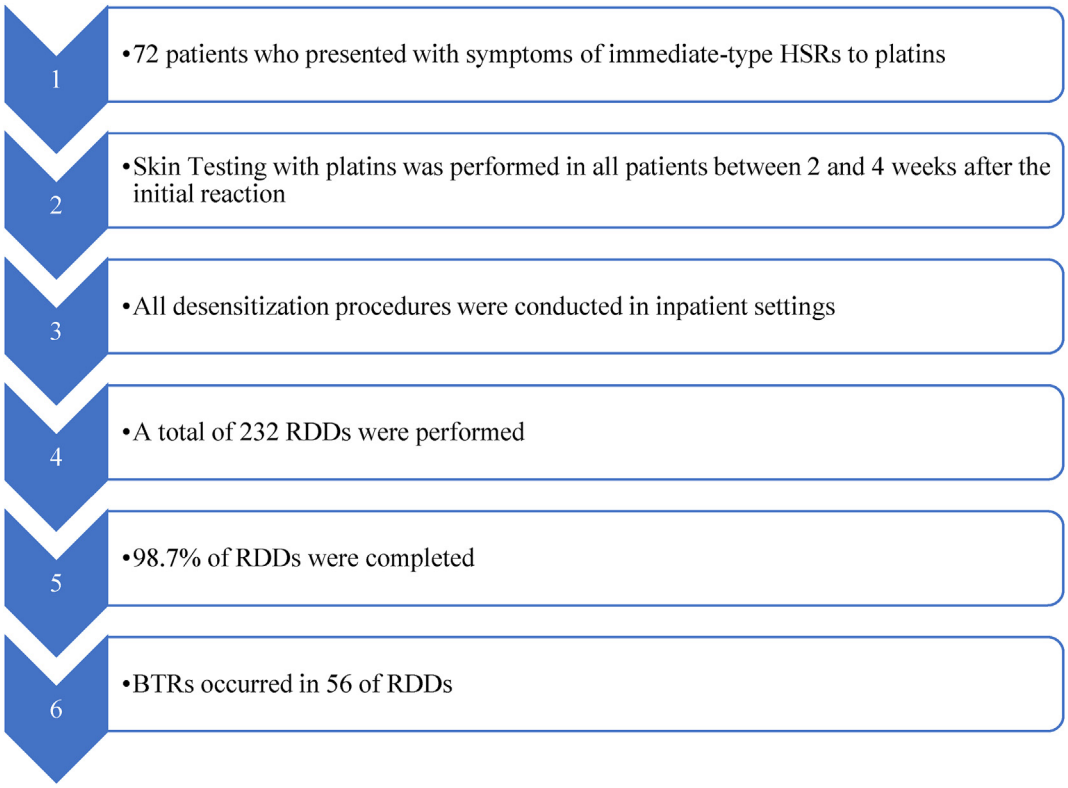

Fig. 1 The flow diagram of the study

Evaluation of atopy

Skin prick tests were performed using a common inhalant allergen panel (Allergopharma, Stockholm, Sweden). The positive and negative controls used were histamine (10 mg/mL) and phenolated glycerol saline, respectively. A mean wheal diameter of ≥3 mm obtained with the control solution was considered positive.

Serum tryptase measurement

Serum tryptase was measured using an enzyme-linked immunosorbent assay (ELISA) radioimmunoassay (ImmunoCAP 100) in blood samples taken at the basal level and as early as within 30 min during BTR. The basal level is normally less than 11.5 µg/L. A significant elevation in tryptase was defined based on the following equation: baseline tryptase multiplied by 1.2 plus 2 µg/L.[15]

Skin testing with platins

Skin testing with platins was performed in all patients between 2 and 4 weeks after the initial reaction. We started the procedure with a SPT, using the undiluted form of the drug, as the following concentrations: 10 mg/mL, 5 mg/mL, 1 mg/mL for carboplatin, oxaliplatin, and cisplatin, respectively. If SPT was negative, IDT was performed starting from 1:100 of the target concentration, and if the result was negative, it was continued with 1:10-1:1concentrations. The IDT was regarded as positive if the initial wheal increased by at least 3 mm in diameter and was surrounded by erythema after 20 min.[16] If the drug skin test was positive on SPT or 1:100 or 1:10 dilutions of IDT, we considered it as a strongly positive skin test.[5,8,17]

Desensitization protocol

The 12-step protocol with 3 dilutions of the target dose of drug-containing X/100, X/10, and X mg, respectively, were diluted in 250 mL of 5% dextrose or 0.9% saline. For patients with Grade 3 reactions with respiratory or cardiac arrest, the protocol was modified as a 16-step protocol by adding a fourth bag with X/1000 dilution. As an experienced department in RDD, we provided one-to-one, desensitization-trained nursing care for each desensitization.[5,12,17] Written informed consent was obtained before each desensitization procedure.

All desensitization procedures were conducted in inpatient settings using glucocorticoids (methylprednisolone 16–40 mg intravenously according to the patients' premedication), H_1 (pheniramine 45.5 mg intravenously), and H_2 antihistamine (famotidine 20 mg or ranitidine 50 mg intravenously) premedication, 30 min before starting the desensitization, which is the routine premedication suggestion of BWH's RDD protocol.[5,17] Acetaminophen was added to the desensitization protocol for patients who presented with fever/chills as a component of the clinical HSR. For BTR during RDD, the infusion was suspended and the reaction was treated. After the reaction was resolved, the protocol was completed. For subsequent desensitizations, additional premedication was added before the step where the previous reaction occurred. For patients with cutaneous reactions or bronchospasm during initial desensitization, the protocol was adjusted by adding aspirin and montelukast, respectively, to the premedication regimen, given the data regarding their benefit in patients with such symptoms.[18] Beta-adrenergic blocking medications were withheld for 24 h before desensitization.

Statistical analysis

All statistical analyses were performed using the SPSS for Windows 11.5 software package (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to assess the assumption of normality. Normally distributed continuous variables are expressed as mean ± standard deviation, and continuous variables that did not have normal distribution are expressed as median (minimum-maximum). Comparisons of variables between groups were performed using Student's t-test/Mann-Whitney *U* test and one-way analysis of variance (ANOVA)/Kruskal-Wallis test. Categorical variables are presented as frequencies (n) and percentages (%). For the analyses of risk factors for BTRs, categorical variables were compared using Fisher's exact test or the Pearson's Chi-square (χ^2) test, as appropriate. Bivariate analysis of the potential risk factors was performed, and P-values less than 0.05 were considered statistically significant. Univariate logistic regression analysis was used to analyze the risk factors for BTRs. The variables that were considered in the analyses for BTR were sex, age, previous platin infusions, the severity of initial HRS, atopy, asthma history, comorbidities, skin tests with platins, platin agents, number of RDDs, and baseline tryptase levels. A two-sided p-value of $\leq$0.05 was considered statistically significant. A multivariate logistic regression model was used to predict potential risk factors of BTRs. The variables that had a significance level of $\leq$0.25 from the univariate analysis were identified as candidate variables for the multivariate model. A multivariate logistic regression model was created using the stepwise method. In this method, variables that were not significant in multivariate logistic regression analysis did not remain in the model. The variables that were significant in the univariate logistic regression analysis but were not significant in the multivariate model were not included in the table. Therefore, multiple logistic regression results for age and baseline tryptase cannot be presented.

RESULTS

The study comprised 65 women and 7 men (mean age 57.78 ± 8.73 years). The clinical characteristics of the subjects and clinical characteristics according to platinum compound HSRs are detailed in Tables 1 and 2. Three patients were

	Patients, n (%)
Age (years) (mean± SD)	57.78 ± 8.73
Sex	
Female	65 (90.3%)
Male	7 (9.7%)
Atopy	
Atopic	3 (4.2%)
Non-atopic	40 (55.5%)
ND	29 (40.3%)
Asthma as comorbid disease	
Yes	10 (13.9%)
No	62 (86.1%)
Implicated platins	
Carboplatin	38 (52.7%)
Cisplatin	13 (18.1%)
Oxaliplatin	21 (29.2%)
Diagnosis	
Ovarian Cancer	38 (52.8%)
Colorectal Cancer	17 (23.6%)
Lung Cancer	9 (12.5%)
Others	8 (11.1%)

Table 1. The clinical characteristics of the study group

	Carboplatin	Oxaliplatin	Cisplatin	p-value
Drug skin test*				**0.008**
Negative/weakly positive	4 (11.1%)[a]	9 (47.4%)[b]	5 (38.5%)[a,b]	
Strongly positive	32 (88.9%)[a]	10 (52.6%)[b]	8 (61.5%)[a,b]	
Sex*				**0.003**
Male	1 (2.6%)[a]	1 (4.8%)[a]	5 (38.5%)[b]	
Female	37 (97.4%)[a]	20 (95.2%)[a]	8 (61.5%)[b]	
Numbers of platin infusions**	6.0 (1.0–20.0)	3.0 (1.0–11.0)	3.0 (1.0–15.0)	**0.027**
Reaction severity Initial HSRs*				**0.096**
Grade 1	1 (2.6%)	1 (4.8%)	3 (23.1%)	
Grade 2	19 (50.0%)	14 (66.7%)	7 (53.8%)	
Grade 3	18 (47.4%)	6 (28.5%)	3 (23.1%)	

Table 2. Clinical characteristics of the patients according to HSRs to platins. **n (%).** median (minimum-maximum)*

positive to pollen on SPTs. Twenty-nine patients were not evaluated for atopy, and there were no results of total IgE and specific IgE in these patients. The most prevalent diagnosis in the study population was ovarian cancer (n = 38, 52.8%), followed by colorectal (n = 17, 23.6%) and lung (n = 9, 12.5%) malignancies. Among all platin chemotherapeutics, carboplatin was the most frequently responsible for HSRs. During the chemotherapy process, patients reacted at the fifth recurrent infusion (median: 5, min:1, max:20). There was a significant difference in terms of reacted cycles between carboplatin, oxaliplatin, and cisplatin (p = 0.027). These median values were 6 (1–20), 3 (1–15), and 3 (1–11) for carboplatin, cisplatin, and oxaliplatin, respectively. According to the results of pairwise comparisons, carboplatin and cisplatin were found to be different from each other. Reactions to cisplatin or oxaliplatin occurred at earlier cycles than with carboplatin.

The majority of initial HSRs were grade 2 (n = 40, 55.6%) and 3 (n = 27, 37.5%); only 6.9% (n = 5) were grade 1. In terms of clinical presentation, skin involvement was the most prominent (n = 65, 90.3%), followed by respiratory symptoms.

Skin prick tests with the implicated platin were performed in 68/72 (94.4%) patients. Skin tests could not be performed on 4 (5.6%) patients because of the use of high-dose systemic steroids and antihistamines, limitations in timing, or other non-clinical reasons (such as patients' preference). Twenty-one (30.9%, 21/68) patients had positive SPTs. Among 47 (69.1%) patients whose SPT was negative, IDT was performed. Thirty-three (70.2%) of these patients were positive for IDT and 14 (29.8%) were negative. Positivity with 1/100, 1/10, and 1/1 IDT dilutions of platins positivity were observed in 21 (63.6%), 8 (24.2%), and 4 (12.1%) patients, respectively. Twelve of 38 (31.6%) patients on carboplatin, 6 of 13 (46.2%) patients on cisplatin, and 3 of 19 (15.8%) patients on oxaliplatin were positive in SPTs, respectively. In addition, 52.6% of patients on carboplatin, 42.9% of patients on oxaliplatin, and 30.8% of patients on cisplatin had positive IDTs, respectively. There was no difference among the platins in terms of skin test positivity, either SPT or IDT (p = 0.113). Patients with grade 1, 2, and 3 initial HSRs had positive platin skin test results at rates of 80%, 74%, and 88%, respectively. There was no statistical difference between the severity of the initial HSR and the positivity of the drug skin test (p = 0.38). If the initial HSR was grade 2 or grade 3, even if skin tests were negative, the patients were desensitized.

As depicted in Fig. 2a and b, 39 of 72 patients tolerated RDD perfectly without any reaction. In 45.8% (n = 33) of patients, BTR was experienced and among them, 64% (21/33) had only one BTR. Four (12%), five (15%), and 2 (6%) of 33 patients had 2, 3, and 4 BTRs during RDDs, respectively. Only 1 (3%) patient had 5 BTRs during RDDs (Fig. 2a and b). A total of 232 RDDs were performed in 72 patients and 98.7% of these desensitizations were completed. The median number of RDDs was 2 (minimum:1, maximum:10). Breakthrough reactions occurred in 56

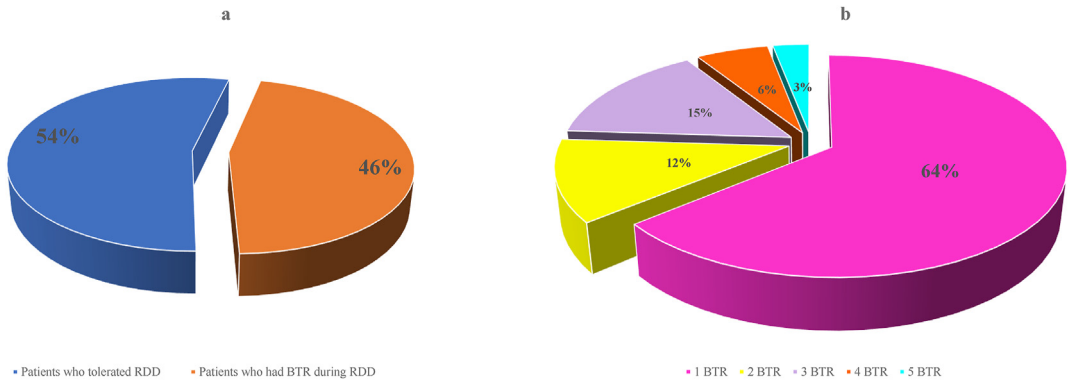

Fig. 2 a: Percentage of patients who tolerated RDD or had BTR during RDD, **b:** Percentage of patients who had one or more than one BTR during RDD

of these desensitizations (grade 1 n = 14, 25%; grade 2 n = 32, 57%; grade 3 n = 10, 18%). Breakthrough reactions were seen in 35 of 134 RDDs performed with carboplatin. Six BTRs occurred in 42 RDDs performed with cisplatin. Fifty-six RDDs were performed with oxaliplatin, and 15 BTRs occurred.

In general, most of the reactions during RDDs were milder than the initial reactions. Most BTRs occurred during the first RDD (n = 43, 77%). There were no BTRs during the infusion of bag 1; the majority (73%) of BTRs occurred during the infusion of the last bag of the protocol. Three RDDs could not be completed in 2 patients with grade 3 BTRs to carboplatin and oxaliplatin, respectively. The first patient with a positive skin test to carboplatin reacted at the eighth step, quickly developing generalized flushing, followed by severe hypotension and hypoxia. Her physician changed the treatment protocol. The second patient had a history of oxaliplatin HSR, but a skin test could not be performed (histamine unresponsive). During the first RDD, at the 12th step, she developed throat tightness, shortness of breath, and numbness. Despite treatment for the BTR, the procedure could not be completed. During the second RDD, she had a similar BTR to the first reaction, consequently, the patient was unwilling to continue with further desensitization.

Six of 15 patients in whom intramuscular epinephrine 0.5 cc (1 mg/mL) was administered had severe BTRs, 57 patients had recorded baseline tryptase levels (mean: 2.80 µg/L, min: 1-max: 9.96) and tryptase levels were measured both at baseline and during BTRs in 33 patients. A significant elevation in tryptase levels (20% of baseline + 2 µg/L) was found in 21 patients during BTRs with a mean of tryptase levels 6.59 (min: 2.07, max: 22.9). BTRs were more severe in patients with significantly elevated tryptase levels ($p = 0.042$). The tryptase level of 5 patients was over 11.5 µg/L during BTR. Two of these 5 patients had Grade 2 BTRs and the other 3 had Grade 3 BTRs.

The rate of cutaneous reactions during BTRs was higher in patients with positive skin tests ($p = 0.007$). BTRs were more severe in patients with positive SPTs or 1:100 or 1:10 dilutions of IDT ($p = 0.014$). In patients with positive 1:1 dilutions of IDT, no BTR was observed during RDD.

Univariate logistic regression analyses were performed with variables of sex, age, drug cycle, initial HSR grade, asthma/allergic disease history, comorbid diseases (thyroid, cardiac, psychologic), and drug skin tests to determine the risk factors for BTR. As a result of univariate logistic regression analysis, a multiple logistic model was established with "age," "psychological comorbidity," "drug skin test" variables, with p-values of <0.25. Although psychological comorbidity was only slightly significant, it remained in the multiple logistic model. Therefore, we determined that when "drug skin test" values were adjusted in terms of psychological comorbidity, a strongly positive drug skin test increased the risk of BTR 5.058 times (OR = 5.058, 95% CI: [1.371–18.665]; $p = 0.015$). There was no significant association between BTRs and age, drug cycle, sex, comorbidities, or atopy (Tables 3 and 4). A risk analysis could not be performed to determine any difference in risk factors according to the intensity such as positivity on IDT 1/100

and IDT 1/10 because the number of patients in the skin test subgroups was small.

DISCUSSION

In this retrospective study, we reported the outcomes, safety, efficacy of RDD, and risk factors of BTRs in a single center. Throughout the study period, a total of 72 patients with platin-reactive cancer underwent 232 desensitization procedures. BTRs occurred in 56 of these desensitizations (24.1%) (grade 1 n = 14, 25%; grade 2 n = 32, 57%; grade 3 n = 10, 18%).

One of the large European series of 1471 RDDs with chemotherapeutics including platins and monoclonal antibodies was performed in Portugal by Caiado et al.[5] There were 136 platin-reactive patients in the cohort and 689 RDDs were performed with these agents. Most of the patients were female (79.8%) because many patients had gynecologic and breast cancers. A prospective study from Spain that had a larger cohort with 188 platin-reactive patients and includes well-characterized patients by using DPT as a part of the assessment, reported 399 RDDs in 104 platin-reactive patients.[2]

Caiado et al noticed that the median infusion number was 7 n for cisplatin, 9 for carboplatin, and 10 for oxaliplatin.[5] Their initial HSRs were moderate to severe (n = 237, 87%), with only 13% (n = 35) as mild, and skin involvement was present in most patients (n = 201, 74%), even in grade 3 HSRs (n = 29, 51.8%). A study, including 67 patients with stage-IV colorectal cancer and oxaliplatin hypersensitivity, reported that initial HSRs occurred within the first hour of oxaliplatin administration and were moderate or severe (Grade 2 or 3) in 60% (40/67), including 5/40 patients presenting with anaphylactic shock and cardiovascular collapse and were Grade 1 in 40% (27/67) of patients. Patients received a median of 11 uneventful oxaliplatin sessions before the initial HSR.[19] In our study, HSRs to oxaliplatin occurred in the median third cycle. The rate of HSRs to platinum compounds usually increases after six doses, but it can be also seen before the sixth dose with a rate of 1%.[3] HSRs to platin agents occurred at the median fifth cycle (min-max:1–20) in our patients, which was earlier in comparison with previous studies.[3,5,17] Some patients came from different hospitals and even different cities and we received information about the numbers of previous platin exposure directly from the patients. Besides, some patients have long-term remission before recurrence of the diseases. Therefore, difficulties in remembering exact exposure numbers and recall bias might affect data regarding the timing of occurrence of HSRs in our study. Indeed, comparing the severity and development cycle of HSRs among studies can be challenging. It is necessary to consider the cancer type and stage, the experience of the infusion team in the management of HSR treatment, and the awareness rate of oncologists about HSRs leading to the referral of patients to an allergist at an earlier stage.

In the present study, skin tests were performed on 68 of 72 patients (94.4%) and 79.4% of the patients (54/68) were positive on skin tests to culprit platins, 21/68 had positive prick tests, and 33 of 68 patients had positive IDTs. Castells et al reported that 53 patients were skin test-positive among 60 patients who were referred for previous HSRs to carboplatin, and two tests became positive after several infusions with a skin test-positivity rate of over 80% in reactive patients; the false-negative rate was as low as 1.5%.[17] Caiado et al performed skin tests with platin in 127 (93.9%) of 136 patients. They reported that most patients (n = 109, 86%) had a positive test result in IDT and 12 (9.5%) patients had positive SPT results.[5] Positivity to platins has been observed mainly in IDTs.[5,12,13] In parallel to these reports, in our previous study, RDDs with platins were performed in 22 patients, 12 (67%) of whom were skin test-positive among 19 skin tests with implicated platins. Positivity was seen mostly on IDTs (n = 8, 66.6%), but a few were positive in the prick test (n = 4, 33.3%).[12]

Patients with a history of HSR to platins or who have a positive drug skin test must not receive the same agent with increased doses of premedication because of the significantly increased possibility of a severe HSR. In addition, switching to another platin agent cannot be recommended because of cross-reactivity between platins; deaths have been reported.[12,20,21] RDD is a valid alternative and patients who are hypersensitive to platins can benefit from RDD. Recent studies showed that RDDs to carboplatin-protected patients against severe HSRs, with a success rate of over 90%.[12,22] The majority of patients perfectly tolerate platin infusion, but 5–10% of patients may still experience BTRs during desensitization.[1,5,13] In a study about BTRs during RDDs, 67% of 413 desensitizations in 98 patients with HSRs to

Variables	RDD without BTRs (n = 39)	BTRs during RDD (n = 33)	P-value
Sex*			0.442
Male	5 (12.8%)	2 (6.1%)	
Female	34 (87.2%)	31 (93.9%)	
Age**	59.13 ± 9.76	56.18 ± 7.16	0.155
Previous platin infusion*			0.980
<10 infusions	32 (82.1%)	27 (81.8%)	
≥10 infusions	7 (17.9%)	6 (18.2%)	
Severity of initial HSR*			0.759
Grade 1	3 (7.7%)	2 (6.1%)	
Grade 2	23 (59%)	17 (51.5%)	
Grade 3	13 (33.3%)	14 (42.4%)	
Atopy*			0.718
Yes	1 (2.6%)	2 (6.1%)	
No	23 (59%)	17 (51.5%)	
ND	15 (38.5%)	14 (42.4%)	
Asthma history*			0.496
Yes	4 (10.3%)	6 (18.2%)	
No	35 (89.7%)	27 (81.8%)	
Cardiac comorbidity*			0.936
Yes	15 (38.5%)	13 (39.4%)	
No	24 (61.5%)	20 (60.6%)	
Psychological comorbidity*			**0.052*****
Yes	3 (7.7%)	8 (24.2%)	
No	36 (92.3%)	25 (75.8%)	
Thyroid comorbidity*			0.590
Yes	1 (2.6%)	2 (6.1%)	
No	38 (97.4%)	31 (93.9%)	
Skin tests with platins******			**0.014**
Strongly positive	22 (61.1%)	28 (87.5%)	
Weakly positive/negative	14 (38.9%)	4 (12.5%)	

Table 3. Comparisons for breakthrough reactions. *ND: not done.*n (%).**mean ± SD.*** slightly significant.****Strongly positive skin test: positive on SPT or 1:100 dilution of IDT or 1:10 dilution of IDT. Weakly positive skin test: positive on the 1:1 dilution of IDT*

chemotherapy had no BTRs, 27% had only mild reactions, and the remaining 6% had severe HSRs.[17] On the other hand, Caiado et al. determined that there were 141 BTRs during RDD (9.6% of infusions), 79.4% induced by platins, with the majority having mild reactions (68.8%).[5] Similarly, with the same protocol, RDD was effective (98.7% of 232 RDDs completed), and safe, with 39 of 72 patients experiencing no BTRs during RDD in our experience. Our BTR rate was only 24% (56 of 232 RDDs) and only 18% of these were severe. We identified that most of the reactions were milder than the initial reactions in general and most BTRs occurred during the first RDD (77%). The majority (73%) of BTRs occurred during the infusion of the last bag and last steps of the protocol. These outcomes are similar to those in previous studies.[5,11,12,19,22]

Data specifically reported about risk factors in patients with BTRs during RDD with platins are limited.[2,5,13] Caiado et al provided evidence that increased total IgE levels (>100 U/mL) (OR: 8.24, 95% CI: [2.06–30.02]; p = 0.001) and a high number of platin infusions (>10) (OR: 4.11, 95% CI: [1.17–14.52]; p = 0.03) were risk factors for BTRs

Risk Factors	Univariate Logistic Regression Analysis			Multivariable Logistic Regression Analysis		
	Crude OR	95% CI	p-value	Adjusted OR	95% CI	p-value
Sex						
Female	2.279	0.412–12.609	0.345			
Age	0.961	0.909–1.015	0.156	–	–	–
Drug cycle						
≥10 infusions	1.016	0.305–3.389	0.980			
Severity of initial HSR						
Grade 1						
Grade 2	1.109	0.167–7.382	0.915			
Grade 3	1.615	0.232–11.263	0.628			
Asthma/Allergic disease history						
Yes	1.944	0.499–7.584	0.338			
Cardiac comorbidity						
Yes	1.040	0.402–2.691	0.936			
Thyroid comorbidity						
Yes	2.452	0.212–28.321	0.473			
Psychological comorbidity						
Yes	3.840	0.927–15.912	0.064	3.847	0.795–18.613	0.094
Baseline tryptase	0.764	0.524–1.114	0.161	–	–	–
Drugs						
Carboplatin						
Oxaliplatin	0.554	0.187–1.642	0.287			
Cisplatin	0.563	0.155–2.035	0.381			
RDD number	1.015	0.845–1.219	0.876			
Skin tests with platins						
Strongly positive*	4.455	1.284–15.449	0.019	5.058**	1.371–18.665	0.015

Table 4. Logistic regression results. **NOTE: Strongly positive skin test: positive on SPT or 1:100 dilution of IDT or 1:10 dilution of IDT.**The risk of BTR was 5.058 times higher in the strongly positive skin test group compared to those who were in the weakly positive/negative skin test group*

during RDD. They commented that an elevated total IgE in patients undergoing RDD could be a helpful marker for identifying high-risk patients who were platin-reactive, but there was no significant association between BTRs and age, sex, highly positive skin test results to the culprit drug, or atopy.[5] In this study, unlike ours, SPT positivity was not a risk factor for BTR, which may be due to the low BTR rate in that study compared with our study (16.3% vs. 24%) or the difference in distribution between platinum subgroups (most of their patients are reactive to oxaliplatin). In another study, the authors determined that the severity of the initial HSR (OR: 17.94, 95% CI: [1.78–181.68]; p = 0.015), history of

drug allergy (OR: 7.83, 95% CI: [1.48–41.44]; p = 0.016), and previous high exposure to the chemotherapeutic agent (OR: 1.14, 95% CI: [1.01–1.28]; p = 0.035) increased the risk of Grade 2 and 3 BTRs.[13] In a recent study, levels of soluble FcεRI receptor <2 ng/mL were found to be a risk factor for BTR. The authors interpreted the finding as sFcεRIs bound IgEs, thus inhibiting the binding of IgE to the mast cell surface FcεRI and activation of mast cells, so the baseline high level of sFcεRI had a protective effect from mast cell activation.[23] Madrigal-Burgaleta et al found that atopy (OR: 2.16, 95% CI: [1.5–14.06]; p = 0.03) and positive SPTs (OR: 4.01, 95% CI: [1.76–10.34]; p = 0.01) were risk factors for BTRs.[2] Supporting these data, in our study, strongly positive skin tests, including SPT and IDT, with more diluted solutions of culprit platin increased the risk for BTR but age, drug cycle, sex or atopy were not risk factors.

Our study has some advantages and disadvantages. We were able to perform skin tests with implicated platins in the majority of the patients. Our study is among those with the highest rates of drug skin tests performed before RDD. Most of the patients had baseline tryptase levels. Measurements of tryptase levels both basal and during BTR could be performed in half of the study group, which was another advantage because this measurement has been made in only on a limited number of studies in which few subjects were subjected to tryptase measurements.[5,23] Some types of BTRs occurred in 45.8% of the patients; however, we were able to complete RDD successfully in the majority of cases. We considered that this high success rate is important for such a high-risk technique and seems to be related to the experience of our center for drug RDD for making necessary adjustments in repetitive RDDs according to patients' reactions. The retrospective nature of this study was a limitation. We are aware that the drug provocation test (DPT) is an essential diagnostic technique for HSRs to chemotherapeutics as other drugs. It rules out events other than HSRs thereby preventing unnecessary desensitization procedures.[8,10,24,25] However, we could not perform DPT as a part of the diagnostic approach, which is also a limitation of our study. The lack of local facilities for the implementation of DPT in our clinic prevented us from performing DPT. Using skin tests as the only diagnostic tool and the presence of patients with negative skin tests without OPT could overestimate the efficacy and safety of RDD. However, as an experienced allergy clinic in drug allergy and desensitization, we are confident in using clinical risk assessment criteria.

In conclusion, this retrospective study from a tertiary allergy clinic demonstrated that carboplatin was the most frequently responsible platin among platins for HSRs. HSRs to platins were observed in earlier cycles of these drugs and skin involvement was the most frequent clinical presentation. Additionally, our findings showed that there was no difference in terms of skin test positivity among platinum agents and there was no association between skin test positivity and the severity of the initial HSR. In our experience, RDD was safe and effective based on the high rate of completed RDDs and drug skin test positivity, on prick and 1:100-1:10 dilutions of IDT was a potential marker for identifying high-risk patients who would have BTRs during RDDs. Defining risk factors for BTRs during RDD will help to optimize the management of future desensitizations with platins by taking necessary and timely precautions.

Abbreviations

BTR: Breakthrough reaction, HSR: Hypersensitivity reaction, IDT: Intradermal test, Ig-E: Immunoglobulin-E, RDD: Rapid drug desensitization, SPT: Skin prick test.

Ethics approval and consent to participate

The local ethics committee of Ankara University Medical School approved the study and written informed-consent was obtained from all subjects. (Ethics committee number I7-416-20).

Authors' consent for publication

Please find enclosed the manuscript 'Rapid Drug Desensitization with Platin-based Chemotherapy: Analysis of Risk Factors for Breakthrough Reactions" for your journal, World Allergy Organization Journal" for consideration of publication. This study provides information regarding the rapid drug desensitization to platins and associated risk factors for breakthrough reactions. All of the authors concur with the submission of this manuscript to World Allergy Organization Journal, and none of the data of this study has been published or is under consideration for publication elsewhere.

The authors declare that they have followed the protocols of their work centre on the publication of patient data and that the patients included in the study received sufficient information and gave their informed consent in writing to participate in that study.

Authors' contributions
All authors are involved in the collection of the data and the writing of the manuscript. All authors read and approved the final manuscript.

Availability of data and materials
Data are available as printed material and as electronic files in the hospital computer. Patients' data protection.

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Declaration of competing interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author details
[a]Division of Immunology and Allergy, Department of Chest Diseases, Ankara University School of Medicine, Ankara, Turkey. [b]Department of Biostatistics and Medical Informatics, Manisa Celal Bayar University School of Medicine, Manisa, Turkey.

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