

# Rapid Drug Desensitization with Chemotherapeutics (Platins, Taxanes, and Others): A Single-Center Retrospective Study

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## Keywords

Rapid drug desensitization · Hypersensitivity reactions · Chemotherapeutics

## Abstract

**Background:** Rapid drug desensitization (RDD) induces a temporary tolerance to chemotherapeutics that induce hypersensitivity reactions (HSRs). **Purpose:** Our objective is to report our experience with RDD to platins, taxanes, etoposide, doxorubicin, and irinotecan. **Methods:** The study was conducted as a retrospective chart review of patients with symptoms of HSRs to chemotherapeutics. HSRs were classified as grade I, II, or III, based on their severity. Skin prick/intradermal tests were performed with implicated chemotherapeutics. A 12-step RDD protocol was used. **Results:** The study consisted of 38 women and 3 men (mean age  $53.3 \pm 11.6$  years). Patients had ovarian ( $n = 13$ , 31.8%), breast ( $n = 10$ , 24.4%), colon ( $n = 7$ , 17%), lung ( $n = 4$ , 9.8%), and other cancers ( $n = 7$ ; endometrial sarcoma, testicular cancer, uterine cancer, ampulla of Vater tumor, choledochal tumor, peritonitis carcinomatosa, and Merkel cell carcinoma,  $n = 1$ , respectively). Twenty-two patients experienced HSRs to platins, 15 to taxanes, and 4 to other chemotherapeutics (doxorubicin, irinotecan, and etoposide). A total of 122 RDDs

(47 to platins, 52 to taxanes, 23 to other chemotherapeutics) were performed. In 25 (61%) patients no reactions occurred during RDD, but breakthrough reactions developed in 16 patients (39%) with platins ( $n = 11$ ), taxanes ( $n = 3$ ), doxorubicin ( $n = 1$ ), and irinotecan ( $n = 1$ ). RDD procedures could not be completed in only 2 patients with grade II breakthrough reactions to carboplatin and oxaliplatin. **Conclusion:** In our experience, 98.3% of 122 RDDs were completed. We found that RDD was safe and effective in this the largest series of RDD with chemotherapeutics in our country.

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## Introduction

All chemotherapy agents have the potential to cause hypersensitivity reactions (HSRs). The availability and increasingly frequent use of these agents have led to a greater number of cancer survivors. These patients are exposed to multiple courses of the same or similar chemotherapeutics, and increased exposure leads to sensitization and an increase in the incidence of HSRs [1–3].

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When a patient experiences an immediate HSR, the first option is to stop the implicated drug or to switch to an alternative medication that is potentially more toxic or less effective. If the culprit drug is the best medication for the patient, another option that overcomes this hurdle is rapid drug desensitization (RDD). RDD was developed for the delivery of a variety of parenteral drugs, including chemotherapeutics and biologic agents, which cause immediate-type hypersensitivity by inducing temporary tolerance. Several protocols for desensitization to chemotherapeutics and biologics have been generated by different groups, but the 12-step RDD protocol developed at Brigham and Women's Hospital (BWH) is considered the safest and most effective protocol [4–7].

At an established allergy and clinical immunology referral center located in Ankara, Turkey, we have been using the BWH RDD protocol since January 2013 for patients with immediate-type HSRs to biologics and chemotherapeutics. The protocol enables the induction of a temporary tolerance to biologic drugs, but data are limited regarding the use of this protocol outside the USA. We previously reported our experience with RDDs to four biologic agents, including rituximab, infliximab, cetuximab, trastuzumab, and anti-TNF agents [8, 9].

Herein, we aimed to report our experience with RDDs to a number of chemotherapeutics. To our knowledge, this is the largest series of chemotherapeutic desensitizations reported in our country.

## Materials and Methods

### Study Design

The study was conducted as a retrospective chart review of patients with symptoms of HSRs to chemotherapeutics. RDDs with chemotherapeutics between 2012 and 2017 were evaluated. The local ethics committee of the School of Medicine, Ankara University, approved the study and informed consent was obtained from all subjects.

### Subjects

Patients who presented to the Department of Chest Diseases and the Division of Clinical Immunology and Allergy, School of Medicine, Ankara University, with symptoms of immediate-type HSRs to chemotherapeutics were eligible for RDD. As in the BWH-based protocols, immediate HSRs were classified as mild (grade I), moderate (grade II), or severe (grade III), in accordance with Brown's grading system. This allowed us to compare our own data with the original BWH-derived reports. Signs and symptoms of HSRs were defined as cutaneous (flushing, pruritus, urticaria, angioedema), cardiovascular (chest pain, tachycardia, sense of impending doom, presyncope, syncope, and hypotension), respiratory (nasal-ocular symptoms, dyspnea, wheezing, oxygen desaturation, and throat tightness), gastrointestinal (nausea, vomiting, diarrhea, and abdom-

inal pain), and atypical manifestations (fever/chills, back and neck pain, and numbness/weakness). A temperature greater than 38 °C was also classified as a moderate reaction [10].

### Evaluation of Atopy

Skin-prick tests were performed using a common 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 or greater than that obtained with the control solution was considered positive.

### Skin Testing with the Culprit Drug

Patients with a history of immediate HSR underwent skin tests as prick tests and intradermal tests (IDTs) with the implicated drug along with appropriate positive (histamine 10 mg/mL) and negative controls (saline solution). Skin tests were performed at least 2–4 weeks after the initial reaction. For skin prick testing, full-strength chemotherapeutic agents including carboplatin (10 mg/mL), cisplatin (1 mg/mL), or oxaliplatin (5 mg/mL), paclitaxel (6 mg/mL) and docetaxel (10 mg/mL) were applied and read after 15 min. A wheal reaction with a mean diameter 3 mm greater than that of the negative control was considered positive. If negative, the first IDT was performed with 1:100 dilution of full-strength chemotherapeutic agent solution, followed by 1:10 and 1:1 dilutions for platins, but dilutions for IDTs were 1:1,000 and 1:100 for paclitaxel, and 1:1,000, 1:100, and 1:10 for docetaxel. The IDT was regarded as positive if the size of the initial wheal increased by at least 3 mm in diameter and was surrounded by erythema after 20 min [6].

### Desensitization Protocol

The 12-step protocol with three 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 III reactions with respiratory or cardiac arrest, a protocol modification was performed using a 16-step protocol in which a fourth bag was added with X/1,000 dilution, or half doses of the drug were given during the first desensitization and then based on the patient's tolerance; the subsequent desensitization was performed with the total target dose of the drug. As an experienced department in RDD, we provided one-on-one desensitization-trained nursing care for each desensitization [4, 6, 11].

Written informed consent was obtained before each desensitization procedure. All desensitization procedures were conducted in inpatient settings with glucocorticoids, H<sub>1</sub> (pheniramine 45.5 mg, intravenously) and H<sub>2</sub> antihistamine (famotidine 20 mg or ranitidine 50 mg, intravenously) premedication, 30 min before starting the desensitization. Acetaminophen was added to the desensitization protocol for patients who presented with fever/chills as the clinical HSR. For breakthrough reactions during RDD, the infusion was suspended and the reaction treated. After the reaction resolved the protocol was completed. For subsequent desensitizations, additional premedication was added before the step at which the reaction occurred. For patients with cutaneous breakthrough reactions or bronchospasm during initial desensitization, the protocol was adjusted by adding aspirin and montelukast, respectively, to the premedication regimen owing to data regarding their benefit in patients with skin and respiratory symptoms. Beta-adrenergic blocking medications were withheld for 24 h before desensitization [12].

**Table 1.** Demographic and clinical characteristics of the study group

| Case No. | Name | Sex | Age, years | Indications               | Atopy    | Implicated chemo-therapeutics | Skin tests with an implicated drug                       | Reaction occurred |          |                |
|----------|------|-----|------------|---------------------------|----------|-------------------------------|----------------------------------------------------------|-------------------|----------|----------------|
|          |      |     |            |                           |          |                               |                                                          | cycle             | Rx grade | Number of RDDs |
| 1        | BA   | F   | 53         | recurrent ovarian cancer  | negative | carboplatin                   | positive (IDT 0.1 mg/mL)                                 | 6                 | II       | 1              |
| 2        | ST   | F   | 50         | recurrent ovarian cancer  | ND       | carboplatin                   | first positive (IDT 0.1 mg/mL), later skin test negative | 8                 | II       | 4              |
| 3        | SD   | F   | 44         | recurrent ovarian cancer  | ND       | carboplatin                   | ND                                                       | 20                | II       | 3              |
| 4        | MT   | F   | 55         | recurrent ovarian cancer  | ND       | carboplatin                   | positive (prick)                                         | 6                 | III      | 1              |
| 5        | SB   | F   | 55         | lung cancer               | ND       | carboplatin                   | positive (IDT 0.1 mg/mL)                                 | 6                 | III      | 1              |
| 6        | SE   | F   | 57         | recurrent ovarian cancer  | ND       | carboplatin                   | First negative, 2nd RDD positive (prick)                 | 6                 | III      | 4              |
| 7        | NB   | F   | 62         | recurrent ovarian cancer  | negative | carboplatin                   | 1, 2, 3 (negative x3)                                    | 2                 | III      | 4              |
| 8        | ÜS   | F   | 54         | recurrent ovarian cancer  | negative | carboplatin                   | First negative, 2nd positive (IDT 0.1 mg/mL)             | 3                 | II       | 5              |
| 9        | ZU   | F   | 73         | peritonitis carcinomatosa | ND       | carboplatin                   | negative                                                 | 6                 | II       | 1              |
| 10       | LÇ   | F   | 63         | recurrent ovarian cancer  | negative | carboplatin                   | positive (prick)                                         | 7                 | II       | 4              |
| 11       | ET   | F   | 56         | ovarian cancer            | ND       | carboplatin                   | negative                                                 | 1                 | II       | 2              |
| 12       | FG   | F   | 50         | recurrent ovarian cancer  | ND       | carboplatin                   | positive (prick)                                         | 7                 | III      | 1              |
| 13       | VA   | M   | 63         | ampulla of Vater tumor    | negative | cisplatin                     | positive (IDT 0.01 mg/mL)                                | 2                 | I        | 1              |
| 14       | AL   | M   | 60         | lung cancer               | ND       | cisplatin                     | positive (IDT 0.01 mg/mL)                                | 1                 | III      | 2              |
| 15       | AG   | F   | 68         | lung cancer               | ND       | cisplatin                     | negative                                                 | 1                 | II       | 3              |
| 16       | AH   | F   | 57         | choledochal tumor         | ND       | oxaliplatin                   | ND                                                       | 1                 | II       | 2              |
| 17       | SŞ   | F   | 68         | colon cancer              | negative | oxaliplatin                   | negative                                                 | 1                 | II       | 2              |
| 18       | NS   | F   | 56         | recurrent colon cancer    | pollen   | oxaliplatin                   | ND                                                       | 3                 | III      | 1              |
| 19       | RG   | F   | 68         | colon cancer              | negative | oxaliplatin                   | negative                                                 | 1                 | II       | 1              |
| 20       | SE   | F   | 54         | colon cancer              | ND       | oxaliplatin                   | positive (IDT 0.5 mg/mL)                                 | 1                 | II       | 1              |
| 21       | SA   | F   | 36         | colon cancer              | ND       | oxaliplatin                   | negative                                                 | 1                 | III      | 2              |
| 22       | HS   | F   | 62         | colon cancer              | ND       | oxaliplatin                   | positive (IDT 0.5 mg/mL)                                 | 1                 | III      | 1              |
| 23       | ÖŞ   | F   | 45         | breast cancer             | ND       | paclitaxel                    | ND                                                       | 1                 | II       | 4              |
| 24       | Fİ   | F   | 74         | uterine leiomyosarcoma    | negative | paclitaxel                    | ND                                                       | 1                 | II       | 2              |
| 25       | SD   | F   | 43         | ovarian cancer            | ND       | paclitaxel                    | negative                                                 | 1                 | II       | 3              |
| 26       | EE   | F   | 38         | endometrium cancer        | ND       | paclitaxel                    | negative                                                 | 1                 | II       | 1              |
| 27       | BA   | F   | 57         | lung cancer               | negative | paclitaxel                    | negative                                                 | 1                 | III      | 7              |
| 28       | ŞK   | M   | 25         | testicular tumor          | ND       | paclitaxel                    | negative                                                 | 1                 | II       | 5              |
| 29       | GS   | F   | 35         | breast cancer             | ND       | paclitaxel                    | negative                                                 | 1                 | III      | 1              |
| 30       | Gİ   | F   | 68         | breast cancer             | ND       | docetaxel                     | ND                                                       | 1                 | II       | 3              |
| 31       | FA   | F   | 45         | breast cancer             | ND       | docetaxel                     | ND                                                       | 1                 | II       | 7              |
| 32       | AÖ   | F   | 41         | breast cancer             | ND       | docetaxel                     | negative                                                 | 1                 | II       | 2              |
| 33       | PK   | F   | 41         | breast cancer             | pollen   | docetaxel                     | negative                                                 | 1                 | II       | 3              |
| 34       | TB   | F   | 37         | breast cancer             | pollen   | docetaxel                     | negative                                                 | 1                 | III      | 3              |
| 35       | UD   | F   | 57         | breast cancer             | negative | docetaxel                     | positive (IDT 0.01 mg/mL)                                | 1                 | III      | 2              |
| 36       | MÇ   | F   | 42         | breast cancer             | ND       | docetaxel                     | negative                                                 | 1                 | III      | 5              |
| 37       | FY   | F   | 57         | breast cancer             | ND       | docetaxel                     | negative                                                 | 1                 | II       | 4              |
| 38       | LA   | F   | 59         | ovarian cancer            | negative | doxorubicin                   | ND                                                       | 1                 | II       | 6              |
| 39       | SC   | F   | 61         | ovarian cancer            | negative | doxorubicin                   | ND                                                       | 1                 | II       | 5              |
| 40       | ZK   | F   | 35         | colorectal tumor          | ND       | irinotecan                    | ND                                                       | 1                 | II       | 10             |
| 41       | HY   | F   | 64         | Merkel Cell carcinoma     | ND       | etoposide                     | ND                                                       | 1                 | III      | 2              |

RDD, rapid drug desensitization; IDT, intradermal test; Rx, breakthrough reactions; ND, not done.

## Results

The study group comprised 38 women and 3 men (mean age  $53.3 \pm 11.6$  years). The demographic and clinical characteristics of the patients are detailed in Table 1. Ovarian malignancy was the most common cancer type, and platins were the main culprit drugs in our study group, followed by taxanes. A total of 13 patients were

tested for atopy, and 3 resulted positive to pollens. The 41 patients included 28 patients with primary cancers and 13 with recurrent cancer. One patient had separate HSRs to 2 drugs. Patients reacted to platins ( $n = 22$ ; carboplatin [ $n = 12$ ], cisplatin [ $n = 3$ ], and oxaliplatin [ $n = 7$ ]), taxanes ( $n = 15$ ; paclitaxel [ $n = 7$ ] and docetaxel [ $n = 8$ ]), and others ( $n = 4$ ; doxorubicin [ $n = 2$ ], irinotecan [ $n = 1$ ], and etoposide [ $n = 1$ ]).

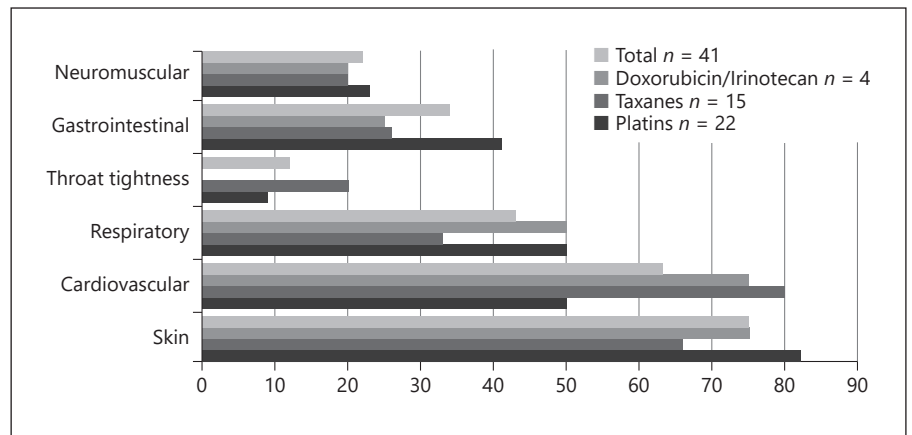


**Fig. 1.** Symptom percentages according to initial HSRs.

### Characteristics of Initial HSRs

Thirteen (60%) of the 22 patients treated with platins experienced an HSR during the recurrent cycles, and generally the third to seventh exposure to the drug. All 15 (100%) patients who were treated with taxanes experienced an HSR during the first cycle. HSRs to doxorubicin ( $n = 2$ ), irinotecan ( $n = 1$ ), and etoposide ( $n = 1$ ) occurred during the first infusion.

Fourteen patients experienced a severe reaction, and 27 presented with mild reactions. The most common platin-induced reactions were cutaneous (92%), respiratory (50%), and cardiovascular (50%). Taxane-induced symptoms were cardiovascular (80%), skin (66%), respiratory (33%), and back pain (13%). When all 41 patients were evaluated, 31 (75%) had skin symptoms, 26 (63%) had cardiovascular symptoms, 18 (43%) had respiratory symptoms, 14 (34%) had gastrointestinal symptoms, and 9 (22%) had neurologic/muscular symptoms (Fig. 1). The distribution of all cases and chemotherapeutics and characteristics of the initial reactions are given in Table 1.

### Skin Test Results

A skin test was performed on 19 of the 22 patients in the platin group, and 12 (67%) had positive results: carboplatin ( $n = 8$ ; prick [ $n = 4$ ], IDT 0.1 mg/mL [ $n = 4$ ]), cisplatin ( $n = 2$ ; both IDT 0.01 mg/mL), and oxaliplatin ( $n = 2$ ; both IDT 0.5 mg/mL). Two patients with carboplatin-negative skin test results were desensitized, and subsequent skin test results turned to positive. Six patients with negative skin test results to platins were desensitized because of the severity of the initial reactions.

Fifteen patients were desensitized to taxanes. Eleven patients underwent a skin test to taxanes, of which 10 were negative (docetaxel [ $n = 5$ ], paclitaxel [ $n = 5$ ]), and

1 was positive (docetaxel, IDT 0.01 mg/mL). Doxorubicin was not used in skin tests because of its high cutaneous toxicity [13].

### Rapid Drug Desensitization

A total of 122 RDDs were performed in 41 patients. A summary of the reactions and RDDs is presented in Figure 2. The patient population predominantly consisted of women with ovarian and breast cancer; 81% were sensitized to platins and taxanes, 38% were desensitized to platins ( $n = 47$  RDDs; carboplatin  $n = 31$ , 25% of RDDs; cisplatin  $n = 6$ , 5% of RDDs; oxaliplatin  $n = 10$ , 8% of RDDs); 43% were desensitized to taxanes ( $n = 52$  RDDs; paclitaxel  $n = 23$ , 19% of RDDs; docetaxel  $n = 29$ , 24% of RDDs), and 19% were desensitized to others (doxorubicin  $n = 11$ , 9% of RDDs; irinotecan  $n = 10$ , 8% of RDDs; etoposide  $n = 2$ , 1% of RDDs). All 122 desensitizations were performed with one-to-one nursing in our allergy clinics.

### Breakthrough Reactions

Sixty-six percent of patients had no breakthrough reactions ( $n = 25$ , 61%) or slight grade I reactions ( $n = 2$ , 5%). The remaining breakthrough reactions were mild grade II reactions ( $n = 11$ , 27% to platins [ $n = 6$ ], taxanes [ $n = 3$ ], and others [ $n = 2$ ]), and severe grade III reactions ( $n = 3$ , 7%), all of which were to carboplatin. Generally, the presented reactions required antihistamines or steroids. No patients were transferred to the medical intensive care unit, intubated, or died. Details of the patients and breakthrough reactions are given in Table 2.

There were three breakthrough reactions with taxanes (paclitaxel  $n = 1$ , docetaxel  $n = 2$ ), despite which all RDD procedures could be completed. The most common symptoms during RDD were cutaneous (44%) and respi-

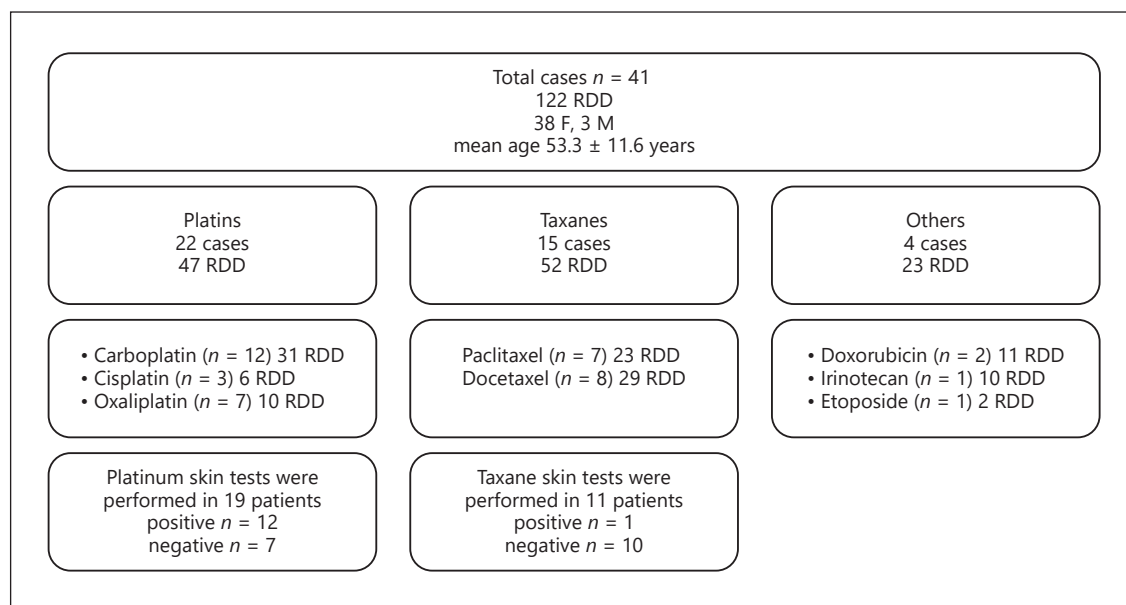


**Fig. 2.** The number of patients who reacted to individual chemotherapeutics and total number of RDDs for each chemotherapeutic.

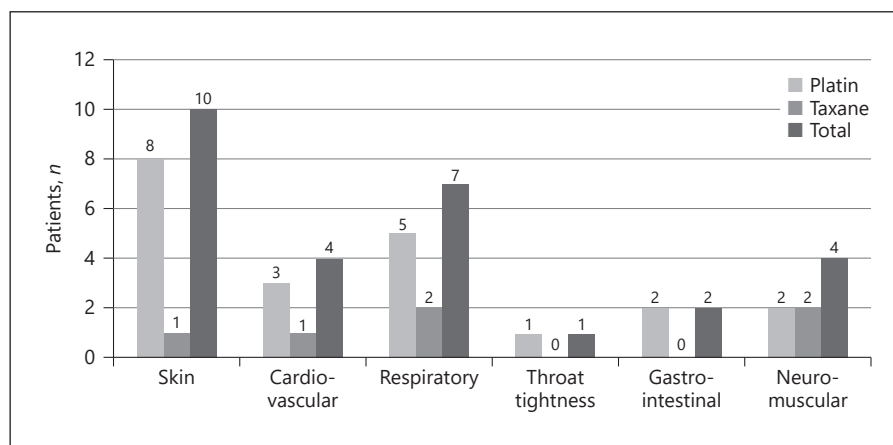


**Fig. 3.** Symptom patterns during desensitization.

ratory (30%). When the whole study group was evaluated, 81% of 122 RDD procedures among 25 out of 41 (61%) patients experienced no reaction during desensitization. A summary of the symptoms during breakthrough reactions is shown in Figure 3.

A total of 23 reactions occurred in 16 patients, with some patients experiencing more than one reaction. Four percent of reactions occurred during solution 1 infusion (steps 1–4), 26% during solution 2 infusion (steps 5–8), and 70% during solution 3 infusion (steps 9–12; Table 2). The majority (60%) occurred during step 12 when patients were receiving the drug at the maximal rate and full

concentration. Skin test was positive in 50% (8/16) of patients with breakthrough reactions and 20% (5/25) of those without breakthrough reactions. Breakthrough reactions were more frequent in patients with a positive skin test ( $p < 0.05$ ;  $\chi^2 = 6.22$ ,  $p = 0.044$ ). In addition, the severity of breakthrough reactions and skin test positivity were related, all 3 patients who had grade III reactions were in the positive skin test group ( $p < 0.05$ ;  $\chi^2$  tests,  $p = 0.023$ ). The difference between the severity grade of RDD and initial reactions was significantly lower ( $p < 0.001$ ) in 31 patients (no breakthrough reaction [Rx] in 25 of them) and no difference was observed in 9 patients (Wilcoxon

**Table 2.** Details of the breakthrough reactions (Rx)

| Patient No. | Name | Indication        | Chemo-therapeutic | Atopy    | Drug skin test                                          | Initial Rx grade | RDD, <i>n</i> | Breakthrough Rx                                                                                                                                             | Rx grade during RDD | Completed   |
|-------------|------|-------------------|-------------------|----------|---------------------------------------------------------|------------------|---------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|-------------|
| 1           | BA   | ovarian cancer    | carboplatin       | negative | positive (IDT 0.1 mg/mL)                                | II               | 1             | 1st RDD, 12th step tachycardia                                                                                                                              | II                  | +           |
| 2           | ST   | ovarian cancer    | carboplatin       | ND       | first positive (IDT 0.1 mg/mL) after skin test negative | II               | 4             | 1st RDD last step urticaria/ angioedema                                                                                                                     | I                   | +           |
| 3           | MT   | ovarian cancer    | carboplatin       | ND       | positive (prick)                                        | III              | 1             | 1st RDD, 8th step grade II Rx, flushing, nausea/vomiting (adrenalin)                                                                                        | II                  | —           |
| 4           | SB   | lung cancer       | carboplatin       | ND       | positive (IDT 0.1 mg/mL)                                | III              | 1             | 1st RDD, 12th step grade II Rx (adrenalin) urticaria, dyspnea, rhinitis, nausea, hypoxia                                                                    | III                 | +           |
| 5           | SE   | ovarian cancer    | carboplatin       | ND       | 1st negative, 2nd RDD positive (prick)                  | III              | 4             | 2nd RDD grade III anaphylaxis (hypoxia, hypotension) – adrenalin<br>3rd RDD planned half dose and 16-step, completed grade III anaphylaxis in the 16th step | III<br>III          | +<br>+1/2   |
| 6           | NB   | ovarian cancer    | carboplatin       | negative | 1, 2, 3 (negative x3)                                   | III              | 4             | First RDD planned half dose, last step fever<br>Second RDD full dose, last step fever                                                                       | II<br>II            | +<br>+      |
| 7           | LÇ   | ovarian cancer    | carboplatin       | negative | positive (prick)                                        | II               | 4             | 1st RDD, 12th step hypoxia-adrenalin<br>2nd and 3rd RDD, flushing grade I Rx                                                                                | III<br>I            | +<br>+      |
| 8           | FG   | ovarian cancer    | carboplatin       | ND       | positive (prick)                                        | III              | 1             | 12th step flushing                                                                                                                                          | I                   | +           |
| 9           | AL   | lung cancer       | cisplatin         | ND       | positive (IDT 0.01 mg/mL)                               | III              | 2             | 2nd RDD, 6th step flushing, tachycardia                                                                                                                     | II                  | +           |
| 10          | AH   | choledochal tumor | oxaliplatin       | ND       | ND                                                      | II               | 2             | 1st RDD, 12th step throat tightness, shortness of breath, numbness, blurred vision<br>2nd RDD similar to 1st RDD – adrenalin                                | II<br>II            | +<br>–      |
| 11          | SŞ   | colon cancer      | oxaliplatin       | negative | negative                                                | II               | 2             | 2nd RDD, dyspnea                                                                                                                                            | II                  | +           |
| 12          | ÖŞ   | breast cancer     | paclitaxel        | ND       | ND                                                      | II               | 4             | 1st RDD dyspnea, tachycardia, back pain                                                                                                                     | II                  | +           |
| 13          | FA   | breast cancer     | docetaxel         | ND       | ND                                                      | II               | 7             | 1st RDD last step dyspnea                                                                                                                                   | II                  | +           |
| 14          | PK   | breast cancer     | docetaxel         | pollen   | negative                                                | II               | 3             | 2nd RDD, 11th step tachycardia<br>3rd RDD, 11th step tachycardia                                                                                            | II<br>II            | +<br>+      |
| 15          | SC   | ovarian cancer    | doxorubicin       | negative | ND                                                      | II               | 5             | 1st RDD, 8th step severe back pain – adrenalin                                                                                                              | II                  | +           |
| 16          | ZK   | colon cancer      | irinotecan        | ND       | ND                                                      | II               | 10            | 1–3 RDD, 7th step fever                                                                                                                                     | II<br>II<br>II      | +<br>+<br>+ |

signed-rank test,  $Z$  value =  $-4.955$ , asymptotic significance [2-tailed] =  $0.000$ ;  $p < 0.001$ ; initial Rx grade min. 1, max. 3, RDD Rx grade min. 0, max. 3; the 50th percentile value [median] was 2 in the initial Rx and 0 in the RDD). A patient who was initially classified as grade II reaction had a grade III reaction during the RDD procedure. Nevertheless, the RDD procedure was successfully completed in this patient. When desensitizations were repeated, the ad-

verse effects were less frequent and less severe because additional steps were added before the step at which the patient reacted, or additional premedication was used.

#### *Failed Desensitizations*

RDD procedures could not be completed in 2 patients with grade II breakthrough reactions to carboplatin and oxaliplatin desensitizations, respectively. These cases were

No. 3 and No. 10 in Table 2. Case No. 3 was a carboplatin-sensitive, recurrent ovarian cancer patient who was skin test positive (prick) to carboplatin. During the first RDD, at the eighth step, she developed flushing, nausea, and vomiting. Case No. 10 had a choledochal tumor and a history of oxaliplatin sensitivity, but a skin test could not be performed (histamine unresponsive). During the first RDD, at the twelfth step, she developed throat tightness, shortness of breath, numbness, and blurred vision; however, the procedure was successfully completed. During the second RDD, she had second breakthrough reactions that were similar to the first reaction. These patients were unwilling to continue with further desensitizations.

## Discussion

Here, we report our experience with 122 RDDs, including 120 (98.3%) successful RDDs in 41 patients who experienced immediate-type HSRs to platins, taxanes, and other chemotherapeutics. RDD is a technique that induces temporary tolerance to a drug, allowing a medication-allergic patient to receive the optimal agent for their disease. We chose to desensitize these patients because there is a need for the culprit drug because of the drug-sensitive recurrent cancer, and/or the implicated drug has low incidence of toxicity in addition to efficacy.

All chemotherapy agents can cause HSRs, but platins and taxanes are the most common chemotherapy agent-involved HSRs [14]. Platin-containing compounds, cisplatin as the first generation and carboplatin as the second generation, are widely used to treat solid tumors in adults, especially for ovarian and lung cancer. The third-generation platinum, oxaliplatin, is widely used for the treatment of metastatic colorectal cancer. These drugs can induce mild-to-severe HSRs, which develop acutely during infusion. Premedication with steroids and/or antihistamines usually prevent mild/moderate reactions, but fail to prevent severe immunoglobulin E (IgE)-mediated reactions [15]. In our study, all patients had a history of immediate HSRs to platinum agents despite premedication with H<sub>1</sub> antihistamines and corticosteroids as standard oncology protocols. Some patients also had breakthrough reactions during desensitization, although they were on more intense premedication.

The timing and clinical presentations of reactions strongly suggest that the mechanism of platin hypersensitivity is based on IgE-induced sensitization. The risk of hypersensitivity is related to the cumulative number of infusions. Typically, reactions occur between the fourth

and eighth courses or after the sixth exposure to platins [16]. Similarly, among our patients who reacted to platins, almost all had a history of multiple platin infusions, except 2 cases who had an unclear history regarding previous chemotherapy regimens. Interestingly, IDT was positive in 1 patient, but it was not tested in the other.

Clinical presentations of HSRs to platins are often similar; the majority had cutaneous symptoms, followed by cardiovascular symptoms, and respiratory and gastrointestinal manifestations. Cutaneous symptoms were also prominent among our patients, followed by cardiovascular and respiratory symptoms.

Skin testing and specific IgE for platins have been used to assess the involvement of IgE in the reaction to predict future reactions, and the assessment of cross-reactivity between carboplatin, cisplatin, and oxaliplatin. However, idiosyncratic reactions to oxaliplatin, including cytokine release syndrome with fevers and chills, have also been reported [16–18]. Castells et al. [1, 5] reported that 53 patients were skin test-positive among 60 patients 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%. In the present study, there were 12 skin test-positive patients among 19 skin tests with implicated platins. Positivity was seen mostly on IDTs, but few were positive on prick test as reported previously [18]. One patient turned to negative after the first desensitization, but 2 patients became skin test-positive in the prick test and 1:100 dilution of IDT, respectively, after the first RDD. We did not systematically evaluate skin tests, but this might be related to the short time interval between reaction and skin testing in these subjects because we were able to complete the remaining 4–5 RDD regimens. Similarly, skin test conversion in either way has been reported in previous experience with RDD [5, 19].

Patients with a history of HSR to platinum agents, or who have a positive skin test result must not receive the same agent with increased doses of premedication because of the significantly increased possibility of a severe HSR in these patients. Additionally, switching to another platinum agent cannot be recommended because deaths have been reported [1, 16]. However, RDD is a valid alternative and patients who are hypersensitive to platins can benefit from RDD [4, 7, 16]. A recent review showed that RDDs to carboplatin protected patients against severe HSR, with a success rate of over 90% [20], which was in line with our success rate (90.9%) for platins. On the other hand, our success rates reached 100% for taxanes, etoposide, doxorubicin, and irinotecan.

Paclitaxel is a widely used antineoplastic agent for the treatment of ovarian, breast, and other solid tumors. Docetaxel is a semisynthetic taxane with similar antimitotic activity to paclitaxel [1, 2]. Premedication with antihistamines and steroids have dramatically decreased the incidence of HSRs to taxanes [14]. Taxanes are an important cause of HSRs in cancer patients although the mechanisms of HSRs to taxanes remain unresolved. Acute onset and the clinical profile of HSRs to taxanes resemble anaphylactic reactions, but skin tests have been negative, indicating complement activation by reactive metabolites or direct mast cells/basophils degranulation [1, 21]. In our trial, taxanes were the second most common chemotherapeutic agent involved in the reactions. As it was in HSRs to platins, the most prominent presenting symptoms of hypersensitivity to taxanes were cutaneous, such as flushing, pruritus, and urticaria. We had only 1 patient with a positive skin test to docetaxel among 11 skin-tested patients with taxanes. A study reported that breakthrough reactions occurred in 12% of desensitizations among a total of 176 desensitizations in 40 patients who presented with HSR after the first or second infusion of paclitaxel or docetaxel. Breakthrough reactions have been less severe than the initial reaction and have not precluded the completion of any treatment course [22]. In our trial, we performed 52 RDDs in 15 patients with taxane-induced immediate HSRs, and only four grade II breakthrough reactions occurred in 3 patients.

Although most desensitization protocols concern platinum compounds or taxanes, in clinical practice, desensitizations to other cytostatic drugs have been attempted [14]. In this context, we performed a total of 23 desensitizations in 4 patients with HSRs to etoposide, doxorubicin, and irinotecan using the same RDD protocol. We completed desensitizations in all subjects despite breakthrough reactions during the procedures. None of these patients were skin tested with the offending agent because of cutaneous toxicity or the lack of data regarding the sensitivity and specificity of skin testing [23].

Besides the effectiveness, RDD has been shown as a safe method to reintroduce the culprit chemotherapeutic agents in patients with cancer even though they experience severe anaphylactic HSRs. Breakthrough symptoms during desensitization have been reported but have been less severe than the initial HSR, and no deaths have been reported in the last 5 years [1, 4, 16]. In the largest series of RDDs reported to date, 67% of 413 desensitizations in 98 patients with HSRs to chemotherapy had no breakthrough reactions, 27% had only mild reactions, and the remaining 6% had severe HSRs [5]. Similarly, with the

same desensitization protocol, 61% of 41 patients experienced no reactions during desensitization in our experience. Our breakthrough reaction rate was 39%, quite similar to that reported by Castells et al. [5]. Platins were the most frequently involved agents in the breakthrough reactions. The cutaneous reaction was the most prevalent breakthrough reaction, followed by respiratory and cardiovascular reactions in our trial. Neuromuscular symptoms, such as severe back pain, numbness, blurred vision, and fever, were also reported by our patients. We had three grade III breakthrough reactions, which only occurred in patients who were carboplatin skin test positive.

When all patients were evaluated, the RDD procedure was not completed in only 2 patients. Consequently, our overall success rate was 98.3%. The routine premedication was steroids and antihistamines, and we also used additional premedication with an H<sub>1</sub> antihistamine, prednisolone, or acetaminophen for the next desensitization procedure according to reactions during the initial desensitization. Furthermore, for patients with cutaneous and respiratory reactions during the initial reaction or desensitization, we adjusted the protocol by adding aspirin and montelukast, respectively.

The retrospective nature of this study was a disadvantage. However, considering the importance of this procedure, we have been systematically collecting details from such patients since our first case of RDD, as we already did for RDD to biologics [9]. Therefore, we are confident that we had all the relevant data.

In conclusion, 98.3% of 122 RDDs were completed. We found that RDD was safe and effective in patients with immediate-type hypersensitivity to chemotherapeutics.

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## Statement of Ethics

The authors have no ethical conflicts to disclose.

## Disclosure Statement

The authors declare that they have no competing interests.

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