

Breakthrough reactions during rapid drug desensitization: Clinical outcome and risk factors



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ABSTRACT

Background: Severe hypersensitivity reactions (HSRs) interfere with the administration of necessary drugs for patients; drug desensitization can be a good alternative strategy. Although rapid drug desensitization (RDD) has been shown to be safe and effective, some patients still experience breakthrough reactions (BTRs) during desensitization.

Objective: We aimed to estimate clinical outcomes of RDD and to identify risk factors for BTR.

Methods: From January 2015 to December 2017, retrospective analysis was done in cancer patients with HSRs to chemotherapy and monoclonal antibody who underwent 3-bag, 12-step RDD in Asan Medical Center.

Results: A total of 58 patients (42 females; mean age, 54.7 ± 11.0) underwent 234 desensitization procedures. The most common underlying malignancy was gynecologic cancer ($n = 26$, 44.8%), and platinum-based drugs were common target drugs (135 cases of 36 patients). Twenty-six of 58 patients (44.8%) experienced 56 BTRs, whereas 178 cases (76.1%) of total desensitization did not show any reactions. Among them, 12 patients (20.7%) had moderate BTRs requiring systemic steroids, and 3 (5.1%) experienced severe BTRs requiring epinephrine administration. Logistic regression analysis revealed more severe initial HSRs ($OR = 17.94$, 95% $CI = 1.78$ – 181.68 , $P = .015$), drug allergy history ($OR = 7.83$, 95% $CI = 1.48$ – 41.44 , $P = .035$), and frequency of exposure to the chemotherapeutic agents ($OR = 1.14$, 95% $CI = 1.01$ – 1.28 , $P = .016$) increased the risk of moderate to severe BTR.

Conclusion: The standardized 12-step protocol for RDD was effective and safe for most patients. Severity of initial HSR, history of drug allergy, and previous high exposure to the chemotherapeutic agent showed a positive correlation with BTR above moderate grade. Studies are needed to propose an individualized protocol according to patient-specific risk assessment.

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Introduction

Recently, new diagnostic tools and therapeutic agents have significantly increased the survival rate of cancer patients compared with that in the past. As the number of cancer survivors exposed to multiple courses of chemotherapy increases, more patients become sensitized to chemotherapeutic agents and suffer from hypersensitivity reactions (HSRs).^{1–3} Hypersensitivity reactions to chemotherapeutic agents range from mild cutaneous

urticaria to severe reactions, such as life-threatening anaphylaxis, and even death.⁴ Most HSRs are unpredictable, such that they threaten the safety of patients; moreover, they can be uncontrollable, and severe HSRs limit the effectiveness of chemotherapy, increase hospital costs, and worsen prognosis.⁵ Thus, understanding HSRs to chemotherapeutic agents and preparing appropriate countermeasures are essential.

In this situation, drug desensitization to a chemotherapeutic agent can be a good alternative strategy. The concept of rapid drug desensitization (RDD) is to administer the causative antigen, starting at a minimal amount and gradually increasing the infusion rate to the target dose, accordingly inducing transient unresponsiveness to culprit drugs essential for optimal therapy.^{6,7} Since it was introduced for patients who experienced penicillin anaphylaxis in the 1940s,⁸ desensitization has shown efficacy and safety for both immunoglobulin E (IgE)-mediated and non-IgE-mediated immediate HSRs, and it has been performed successfully for various antibiotics, antituberculous drugs, biologics, and cytotoxic chemotherapeutic agents.^{5,9}

Among available RDD regimens, the rapid 3-bag 12-step protocol introduced by Castells et al.¹⁰ is widely used. In 2008, 413 desensitization procedures using this method were conducted in 98 patients, of which 94% showed mild or no reactions. Subsequent studies showed that the protocol was safe and effective for most patients, but several patients still experienced breakthrough hypersensitivity reactions (BTRs) during desensitization; hence, these patients could not progress through desensitization. Therefore, understanding and determining the risk factors of BTRs are important.

In 2015, we introduced the 3-bag, 12-step RDD in the Asan Medical Center for patients with difficulty in administering fundamental chemotherapeutic agents because of HSR. In this study, we aimed to estimate the efficacy, safety, and outcomes of RDD, as well as identify the risk factors for BTR that affect desensitization outcome, over 3 years at a single university hospital in Korea.

Methods

Patients and Study Protocol

The data were collected from patients who underwent RDD from January 01, 2015 to December 31, 2017 at Asan Medical Center. After experiencing HSR, the patients were referred to an allergist for desensitization at the discretion of oncology and gynecology clinicians.

We retrospectively reviewed the patients' electronic medical records and obtained the patients' baseline characteristics, such as sex, age, drug allergy history, underlying malignancy, chemotherapy purpose, desensitization target drug, chemotherapy regimen, mean hospital days, desensitization time, and skin test results. Initial HSR details were collected, including symptoms/signs and total number of previous exposures to chemotherapeutic agents. The severity of the initial HSR was classified following Brown's classification of anaphylaxis.¹¹ Mild reactions were characterized as those involving only the skin and subcutaneous tissue; moderate reactions were those involving systemic organs, such as respiratory, cardiovascular, and gastrointestinal organs; severe reactions included those involving systemic organs and changes in vital signs, such as hypoxia, hypotension, and neurologic compromise. Based on the signs and symptoms, HSRs were classified into cutaneous (urticaria, angioedema, flushing, pruritis), upper respiratory (cough, sneezing, nasal congestion), lower respiratory (chest tightness, dyspnea, desaturation), gastrointestinal (nausea, vomiting, abdominal pain), cardiovascular (hypertension, hypotension, tachycardia, arrhythmia), neurologic (dizziness, disorientation, loss of consciousness, sensory abnormality), and other systemic (fever, chill) reactions.

To evaluate the efficacy and safety of RDD, we investigated the frequency and severity of BTRs during desensitization. The severity of BTRs were classified similarly to that of HSRs; mild reaction indicated localized skin reactions that recovered promptly after cessation of the desensitization drug and intravenous antihistamine administration; moderate reaction was indicated by systemic organ involvement with generalized skin rashes that required systemic steroids; and severe BTRs included anaphylaxis or organ involvement with changes in vital signs (hypoxia, hypotension, and neurologic symptoms) occasionally needing epinephrine injections.

Rapid Drug Desensitization Protocol

As previously published by Castells et al.,¹⁰ the 3-bag, 12-step desensitization protocols were used for desensitization, in which the dosage of the drug was gradually increased from 1:100 of the target dose to 1:10 and 1:1.¹⁰ We adapted the protocol to achieve a final infusion rate of 60 mL/h (eTable 1). For patients showing moderate to severe BTRs during the 12-step desensitization protocol, the 16-step (4 bags) protocol was applied.⁵ In every case, patients provided informed consent, and desensitization procedures were conducted in a general ward of oncology or gynecology service with well-trained nursing staff and supervised by the allergist.

Every patient received a standard premedication regimen of 120 to 240 mg oral fexofenadine, 5 to 10 mg oral cetirizine, 10 mg oral lantidine, and 5 to 20 mg intravenous dexamethasone at 12 and 6 hours before desensitization. Thirty minutes before desensitization, patients were administered intravenous chlorpheniramine, dexamethasone, and famotidine. Patients who experienced severe dyspnea during the initial HSR received an additional 10 mg oral montelukast at 6 hours and at 30 minutes before desensitization. The dosages of intravenous dexamethasone varied from 5 to 20 mg, depending on the severity of the initial HSR. In the case of 16-step desensitization, this premedication with antihistamine, montelukast, and dexamethasone was administered at the maximal dose.

Skin Test

Skin prick test (SPT) and intradermal test (IDT) were performed for each culprit chemotherapeutic agent at least 2 weeks after the initial HSRs to minimize false-negative results. For SPT, in accordance with previous studies, nonirritating doses of the tested drugs were prepared, namely, carboplatin 10 mg/mL, cisplatin 1 mg/mL, oxaliplatin 5 mg/mL, rituximab 10 mg/mL, and cetuximab 5 mg/mL. For IDT, carboplatin 1 mg/mL and 10 mg/mL, cisplatin 0.1 mg/mL and 1 mg/mL, oxaliplatin 0.5 mg/mL and 5 mg/mL, rituximab 1 mg/mL and 10 mg/mL, and cetuximab 5 µg/mL were prepared as described in previous studies.^{12–16} Histamine and saline were used as positive and negative controls, respectively. The patients were injected with 0.02 mL skin test solution via the forearm, and IDT results were considered positive if the net wheal, compared with the saline control, was greater than 3 mm with a surrounding flare after 15 minutes.

Statistical Analysis

Statistical analyses were performed with IBM SPSS Statistics (Version 24.0; SPSS Inc., Chicago, IL). Categorical variables are reported as number and percentages, and they were analyzed using the χ^2 test and Fisher's exact test. Continuous variables are reported as mean $\pm$ standard deviation, ranges used the Student's *t* test or Mann Whitney *U* test with a 95% confidence interval. For correlation analysis between ranking scales, such as initial HSR or BTR, Spearman's correlation was used.

To identify the predictors associated with BTRs during RDD, we used logistic regression analysis. We analyzed risk factors in the BTR-positive group as well as moderate to severe-grade BTRs, which was clinically important in real-world practice. After performing univariate analysis of patient's initial reaction variables, including age, sex, symptoms, and severity of initial HSRs (according to Brown's classification), results of skin test, number of previous exposures to the chemotherapeutic agent, and drug allergy history. Variables were considered significant when $P < .05$ in univariate analysis. These variables were not statistically different for each drug class, and further analysis was conducted by multivariate analysis using logistic regression with a backward stepwise selection.

Ethics

The study was approved by the Institutional Review Board of the Ethics Committee of Asan Medical Center (IRB number: 2018-1530).

Results

Baseline Characteristics and Demographic Data

A total of 234 desensitization procedures were performed in 58 patients for 3 years. Baseline characteristics of the study patients are presented in Table 1. The mean age of the patients was 54.7 ± 11.0 years. Forty-two patients (72.4%) were women, of whom 20 (35.1%) had a history of drug allergy. Desensitization was carried out 3.98 ± 2.8 times per person, ranging from 1 to 11 times. The average hospital stay of the patients was 3.98 ± 1.4 days, and the average time taken for the desensitization procedure was 7.8 ± 1.8 hours.

Gynecologic (such as ovarian and cervical cancer) and gastrointestinal cancers (including colon, rectal, and advanced gastric cancers) were the most common cancers among the study patients. Only a few patients had breast cancer ($n = 3$, 5.2%), lung cancer ($n = 1$, 1.7%), and hematologic malignancies (eg, acute myeloid leukemia, diffuse large B cell lymphoma, and primary central nervous system lymphoma, $n = 5$, 8.6%). Most of the patients ($n = 46$, 79.3%) received palliative chemotherapy, but 4 patients (6.9%) were in a curative setting.

Table 1
Basic Characteristics and Demographics of the Study Patients

Characteristics	Value
Total patients (N)	58
Age (years), mean $\pm$ SD	54.7 ± 11.0
Sex: female, N (%)	42 (72.4)
Prior history of drug allergy, N (%)	20 (35.1)
Total no. of desensitization (N)	234
Mean no. of desensitization $\pm$ SD (range)	3.98 ± 2.8 (1–11)
Mean hospital day $\pm$ SD, day	3.98 ± 1.8
Mean time of desensitization $\pm$ SD, hours	7.8 ± 1.8
Type of malignancy, N (%)	
GY (ovarian, cervical, endometrial cancer, etc.)	26 (44.8)
GI (colorectal, cecal ca. AGC, pancreas cancer, etc.)	23 (39.7)
Breast	3 (5.2)
Lung	1 (1.7)
Hematologic (AML, DLBCL, PNCSL, etc.)	5 (8.6)
Purpose of chemotherapy, N (%)	
Curative	4 (6.9)
Adjuvant	7 (12.1)
Neoadjuvant	1 (1.7)
Palliative	46 (79.3)

GY, Gynecologic; GI, Gastrointestinal; AGC, Advanced gastric cancer; AML, Acute myeloid leukemia; DLBCL, Diffuse large B cell lymphoma; PNCSL, Primary central nervous system lymphoma.

Desensitization Target Drugs

Among 234 RDD procedures, platinum-based drugs were the most common target drug, followed by biologic agents. Paclitaxel and other drugs, such as thymoglobulin, ifosfamide, dacarbazine, high-dose methotrexate, and leucovorin, were also used for desensitization. In 1 patient, 4 desensitization procedures for 2 drugs (oxaliplatin and leucovorin) were performed simultaneously (Table 2).

Characteristics of Initial HSRs

In the study patients, 51 (87.9%) experienced moderate to severe initial HSRs, and 7 (12.1%) experienced mild reactions. Cutaneous reactions, such as rash, urticaria, and angioedema, occurred in 49 (85.9%) and 43 patients (75.4%), who also experienced lower respiratory symptoms, such as dyspnea and chest tightness. No statistical difference was seen between the severity of the initial HSRs and drug class of the chemotherapeutic agents (Table 3). Overall, the platinum group developed initial HSRs after an average of 10.3 ± 6.2 (range, 1–30) times of exposure to the previous chemotherapy, whereas biologics and taxanes showed initial HSRs after 1 to 2 times of exposure to chemotherapy, respectively (data not shown).

Skin Test

Because its validity has not been verified by prospective studies, the skin test was not performed routinely but only on feasible patients. Skin prick test and IDT produced the same results in the 18 patients tested, of whom 8, 8, and 2 patients showed negative, positive, and equivocal results, respectively. Moreover, 5 of 7 patients tested by carboplatin, among all platins, had the highest positive ratio, whereas 4 of 5 were negative for cisplatin (eTable 2).

Outcomes of RDD: Characteristics of BTR

A total of 56 BTRs were observed in 26 of 58 patients (44.8%), and the remaining 178 of 234 RDDs (76.1%) did not show any reaction. Mild BTRs were observed in 30 of 234 RDDs (12.8%) in 11 of 58 patients (18.9%), with localized urticaria and flushing being the most common. Moderate BTRs were observed in 21 of 234 RDDs (9.0%) in 12 of 58 patients (20.7%), which recovered immediately after administration of intravenous chlorpheniramine and steroid; thus, the procedure did not interfere with reaching the total target dose. In 5 of 234 RDDs (2.1%) in 3 of 58 patients (5.2%) experiencing severe BTRs, 3 incidents required epinephrine administration, but

Table 2
Number of RDDs Classified by Chemotherapeutic Agent

Target drugs	No. of patients (%) (N = 58)	No. of RDDs (%) (N = 234)	No. of BTR (%) (N = 56)
Platins	36 (62)	135 (58)	46 (82)
Carboplatin	17 of 36 (47)	57 of 135 (42)	31 of 46 (68)
Oxaliplatin	12 of 36 (33)	51 of 135 (38) ^a	13 of 46 (28)
Cisplatin	7 of 36 (20)	27 of 135 (20)	2 of 46 (4)
Biologics	13 (22)	69 (29)	7 (12)
Cetuximab	10 of 13 (77)	50 of 69 (72)	7 of 7 (100)
Rituximab	2 of 13 (15)	8 of 69 (12)	0
Pertuzumab	1 of 13 (8)	11 of 69 (16)	0
Taxanes	5 (8)	18 (8)	1 (2)
Paclitaxel	5 of 5 (100)	18 of 18 (100)	1 of 1 (100)
Other drugs	5 (8)	12 (5)	2 (4)
Dacarbazine	1 of 5 (20)	3 of 12 (25)	1 of 2 (50)
Ifosfamide	1 of 5 (20)	2 of 12 (17)	0
HD-MTX	1 of 5 (20)	5 of 12 (42)	0
Thymoglobulin	1 of 5 (20)	2 of 12 (17)	1 of 2 (50)
Leucovorin	1 of 5 (20)	4 of 12 (33) ^a	0

HD-MTX, high-dose methotrexate; RDD, rapid drug desensitization.

^aIn 1 case, 4 desensitization procedures for 2 drugs (oxaliplatin and leucovorin) were performed simultaneously.

Table 3

Clinical Characteristic of Initial HSR and BTR Classified by Drug

	Platins (N = 36)	Biologics (N = 13)	Taxanes (N = 5)	Others (N = 4)	Total (N = 58)
Severity of initial HSR, N (%)					
Mild	5 (14)	1 (8)	0	1 (25)	7 (12)
Moderate	9 (25)	1 (8)	3 (60)	0	13 (22)
Severe	22 (61)	11 (84)	2 (40)	3 (75)	38 (66)
Severity of BTR, N (%)					
No reaction	17 (47)	9 (70)	4 (80)	2 (50)	32 (55)
Mild	6 (17)	2 (15)	1 (20)	2 (50)	11 (19)
Moderate	10 (28)	2 (15)	0	0	12 (21)
Severe	3 (8)	0	0	0	3 (5)
Symptoms of initial HSR, N (%)					
Cutaneous	30 (83)	11 (85)	5 (100)	3 (75)	49 (85)
Upper respiratory	3 (8)	0	0	0	3 (5)
Lower respiratory	25 (68)	11 (85)	4 (80)	3 (75)	43 (74)
Gastrointestinal	11 (30)	1 (8)	1 (20)	0	13 (22)
Cardiovascular	8 (22)	9 (70)	2 (40)	0	19 (33)
Neuromuscular	7 (19)	3 (23)	1 (20)	0	11 (19)
Other systemic	3 (8)	0	0	0	3 (5)
Symptoms of BTR, N (%)					
Cutaneous	17 (89)	2 (50)	1 (100)	1 (50)	21 (81)
Upper respiratory	4 (21)	0	0	0	4 (15)
Lower respiratory	10 (53)	2 (50)	0	0	12 (46)
Gastrointestinal	8 (42)	2 (50)	0	0	10 (38)
Cardiovascular	4 (21)	0	0	0	4 (15)
Neuromuscular	1 (5)	0	0	0	1 (4)
Other systemic	0	0	0	1 (50)	1 (4)

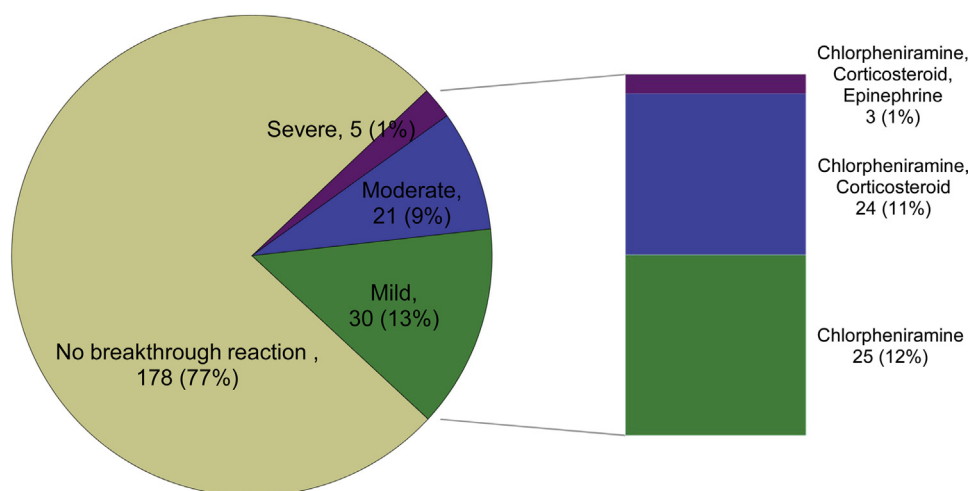
BTR, breakthrough reaction; HSR, hypersensitivity reaction.

no harm was caused to the patients because their symptoms and vital signs all recovered immediately after prompt termination of the drug and administration of chlorpheniramine, steroids, and epinephrine (Fig 1).

All 3 patients had severe BTRs to carboplatin. Case 1 presented rash, dyspnea, sweating, and hypotension during step 8 of the protocol. The symptoms subsided, and vital signs were stabilized after administration of 4 mg intravenous chlorpheniramine, 5 mg intravenous dexamethasone, and 0.3 mg intramuscular epinephrine. Cases 2 and 3 presented dyspnea, desaturation, rash, and pruritis during step 11 of the protocol; and they recovered completely as well after injection of 4 mg intravenous chlorpheniramine, 40 mg intravenous methylprednisolone, and 0.3 mg intramuscular epinephrine. The remaining solutions were administered completely by slow infusion (40 cc/hour), but cases 1 and 2 refused their next desensitization procedures. In case 3, we tried the 4-bag, 16-step protocol, but the remaining dose was not administered because of desaturation and hypertension that occurred in step 11.

Table 3 summarized the clinical characteristics of BTRs. Most patients with BTRs had cutaneous (81%) and lower respiratory (46%) symptoms. Classified by the drug, BTRs occurred in 46 of 135 platin desensitizations (34.1%), in 7 of 69 biologics desensitizations (10.1%), and in 1 case of 18 taxane desensitizations (5.6%) (Table 2, Fig 2A). In 10 of 26 patients of the BTR-positive group, all reactions improved or disappeared during repeated RDDs, and 61 subsequent desensitization procedures did not cause BTRs. However, the remaining 16 patients suffered more than 2 BTRs. Most BTRs occurred during the first desensitization procedure ($n = 20$), at steps 11 or 12 (38 of 56, 67.8%) (Fig 2B); but in 1 patient, the first BTR occurred during the fourth RDD procedure. A total of 3 patients underwent the 4-bag, 16-step desensitization protocol because severe HSRs persisted during the 12-step protocol.

Although 3 patients stopped the desensitization protocol because of severe BTRs, 22 of 58 patients who received RDD were able to complete the chemotherapy schedules (37.9%). Other patients stopped the desensitization because of changes in chemotherapy regimens attributable to progression of underlying disease

**Figure 1.** Number, severity, and management of breakthrough reactions during desensitization.

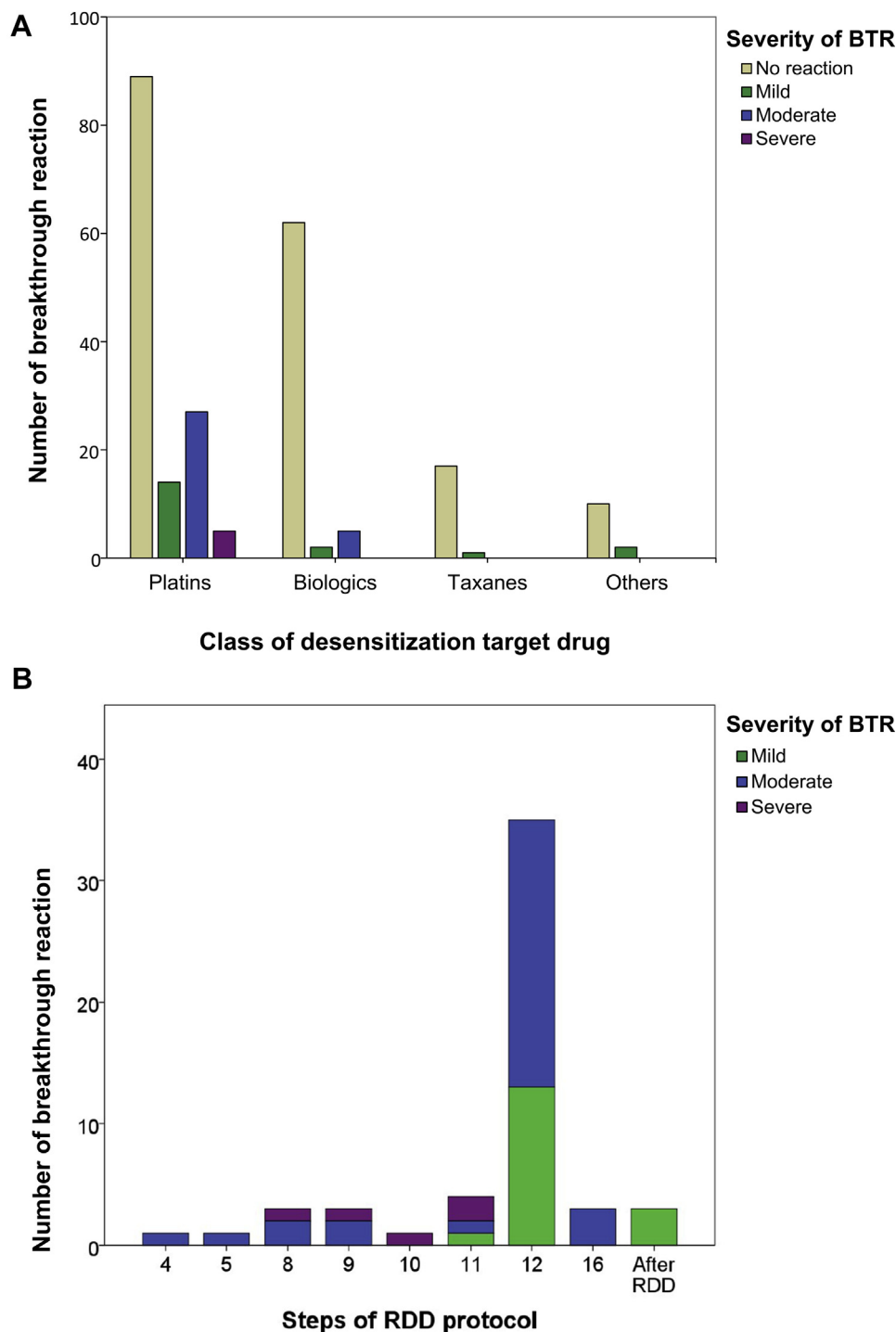


Figure 2. A, Number and severity of breakthrough reactions classified by drug. B, Desensitization step at which breakthrough reaction occurred.

($n = 25$, 43.1%) and chemotherapy side effects ($n = 2$, 3.4%). Of the 6 remaining patients, 3 were not followed up, and 3 continued to receive RDD for their chemotherapy schedules.

Risk Factors for BTR

Table 4 shows clinical characteristics of the patients according to the severity and presence of BTRs. The number of previous exposures to chemotherapeutic agents showed statistical difference in both the BTR-positive and above-moderate-grade BTR groups. In correlation analysis, BTR tended to be severe when the initial HSRs

were severe, as shown by $Rho = 0.350$ in Spearman's correlation analysis (Fig 3).

Table 5 summarizes the results of logistic regression analyses. Additional previous exposure to chemotherapeutic agents, severity of initial HSR, and history of drug allergy were variables associated with an above-moderate-grade BTR, as determined by multivariate analysis. Severe initial HSR and previous high exposure to chemotherapeutic agents were also positively correlated with BTRs. The results of the skin test did not show any statistically significant differences, although it was not performed in all patients.

Table 4
Demographics and Clinical Characteristics of BTR According to Severity

	Presence of BTR		<i>P</i> ^a	Moderate to severe BTR		<i>P</i> ^b
	BTR negative (N = 32)	BTR positive (N = 26)		None or mild BTR (N = 44)	BTR above Moderate (N = 14)	
Total no. of desensitization	117	117		163	71	
Sex: female, n (%)	23 (71.9)	19 (73.1)	.814	31 (70.5)	11 (78.6)	.804
Age, mean ± SD	52.4 ± 11.7	57.6 ± 9.4	.076	53.6 ± 11.2	58.2 ± 9.9	.176
History of drug allergy, n (%)	10 (20.3)	11 (44.0)	.424	14 (31.8)	7 (50.0)	.361
No. of previous cycle, mean ± SD	5.1 ± 6.3	8.6 ± 6.4	.024	5.5 ± 6.0	10.5 ± 6.8	.011
Severity of initial HSR, n (%)			.097			.044
Mild	5 (15.6)	2 (7.7)		7 (15.9)	0 (0)	
Moderate	10 (31.3)	3 (11.5)		12 (27.3)	1 (7.1)	
Severe	17 (53.1)	21 (80.8)		25 (56.8)	13 (92.9)	
Drug class, n (%)			.355			.167
Platins	17 (51.5)	19 (76.0)		24 (54.5)	12 (85.7)	
Biologics	10 (27.3)	4 (16.0)		11 (25.0)	2 (14.3)	
Taxanes	4 (12.1)	1 (4.0)		5 (11.4)	0 (0)	
Others	2 (9.1)	2 (4.0)		4 (9.1)	0 (0)	

BTR, breakthrough reaction; HSR, hypersensitivity reaction.

^aDifference between the BTR-negative and BTR-positive groups.^bDifference between the none or mild BTR and BTR above moderate groups.

Discussion

In this retrospective study, we investigated the outcomes, safety, efficacy of RDD, and risk factors of BTRs over a 3-year period in a single center. Throughout the study period, a total of 58 patients underwent 234 desensitization procedures with 60 drugs. Among them, 26 patients (44.8%) experienced 56 incidents of BTRs, and 15 patients among the 26 patients with BTRs (25.9% of 58 patients) showed 26 incidents of moderate to severe BTRs (11.1% out of 234 RDDs), whereas the 178 RDD procedures did not show any reaction. All BTRs were less severe than the initial HSRs; hence, it did not interfere with the administration of the scheduled chemotherapy. Prior exposure to chemotherapeutic agents, history of drug allergy, and severity of initial HSRs were variables significantly associated with development of moderate-to-severe BTRs.

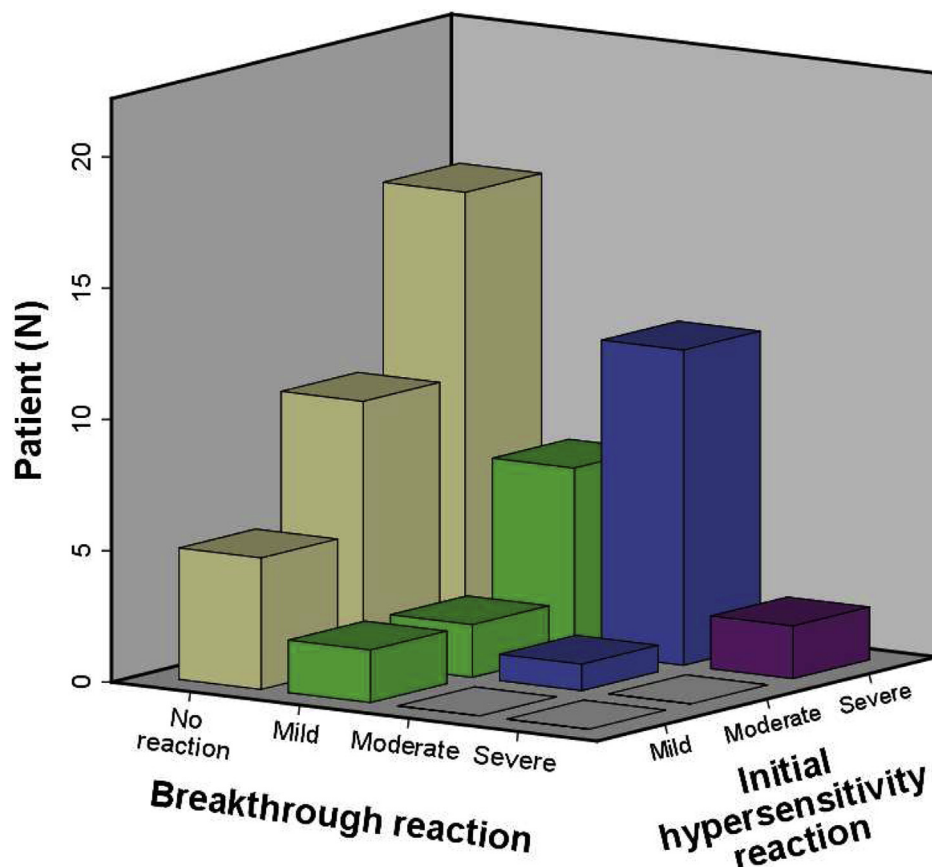
During the last few decades, large-scale studies showed the safety and efficacy of desensitization to various drugs, including cytotoxic chemotherapy agents and monoclonal antibodies, but incidences of BTRs were reported to vary from approximately 10% to 40%,^{10,14,17–20} although the target drug of desensitization and definition BTR severity were inconsistent in previous studies. According to Castells et al,¹⁰ the incidence rate of mild BTRs during rapid desensitization was 26.9% (111 of 413), including absence of chest pain, blood pressure change, dyspnea, hypoxia, desaturation, and throat tightness, whereas that of severe BTRs (including 1 of the above symptoms) was 5.8% (24 of 413).¹⁰ Lee et al¹⁴ reported that 18 of 57 patients showed 30 incidents (11.8%) of BTRs during 255 desensitization, and Cortijo-Casajares et al¹⁷ reported that BTR occurred in 6 of 53 platin desensitization (11%) and that severe reactions occurred only once.¹⁷ In 2014, Kuo et al¹⁸ also reported 25 desensitizations in 13 patients, with 4 patients (30.7%) showing recurrent BTRs.¹⁸ In 2016, Borrás and El-Qutob¹⁹ also reported that in 281 desensitization performed in 53 patients, 39% of patients (n = 21) developed BTRs, of which 11% (n = 5) showed moderate severity (eg, hypotension and dyspnea)¹⁹; Sloane et al²⁰ reported that in 2177 desensitizations performed in 370 patients, 7% (154 incidents) developed moderate-to-severe BTR.²⁰

In this study, approximately 45% of patients (n = 26) experienced 56 BTR incidents. The severity of BTRs was attenuated throughout repeated desensitization procedures, so that full target dose was eventually archived, except in 1 case; however, 15 patients suffered from moderate to severe reactions. There was no death, but 3 patients experienced 5 severe BTRs, whereas 3 incidents required epinephrine administration, suggesting that

desensitization should be closely monitored by experienced medical staff. Among them, a patient who experienced severe reactions to carboplatin was also intolerant of the 16-step desensitization. We found that drug allergy history, the more previous exposure to chemotherapeutic agents, and more severe initial HSRs were expected to increase risk of BTRs over the moderate grade. In 2016, Murray et al²¹ reported that urticaria and labored breathing during initial HSR was not associated with reaction during desensitization,²¹ and we also did not find a particular association of symptoms in the logistic regression analysis. Inconsistent with this study, in a study of 36 patients published in 2018, Mawhirt et al²² reported that desensitization-tolerant groups showed much higher grade 3 to 4 index hypersensitivity reactions.²² However, both studies presented us with difficulty in determining statistical significance because of the insufficient patient numbers; thus, additional follow-up studies are needed to verify the risk factors of BTR.

The development of initial HSRs in the patients of this study was similar to that in a previous research, because platins usually cause HSRs after approximately 6 to 10 cycles of drug exposure, whereas taxanes and monoclonal antibodies cause HSRs after 1 to 2 episodes of drug exposure.^{10,23} Different drug classes showed different clinical characteristics and phenotypes in the development of HSRs, suggesting that heterogeneous mechanisms may have caused the HSRs.²⁴ The BTRs occurred mainly at the first desensitization in steps 11 to 12, which were the last solution of desensitization, and all of the reactions were less severe than the initial HSRs. In addition, even if BTRs did occur, they became less severe or disappeared with repeated occurrences. In some cases, BTRs occurred first at the 2nd through 4th desensitization cycles, although there was no reaction in the first desensitization, thereby indicating that starting desensitization on hospitalization is safe, not only for beginning desensitization for the first time, but also for the first 3 to 4 cycles.

Skin tests were not conducted on all patients because of the timing and difficulty in the preparation of the skin test solution. Previous studies showed conflicting results regarding whether skin tests for taxanes have diagnostic value in predicting the development of HSR,^{25–27} whereas skin tests for platins showed prognostic significance for making decisions regarding desensitization.²⁸ In this study, skin tests were not conducted for taxanes, and we could not find a correlation between positive skin tests for platins and the severity of initial HSRs, as well as BTRs. Generally, platins tend to cause initial HSRs after 4 to 9 cycles of exposure to chemotherapy.^{29,30} Makrilia et al²³ recommended that skin tests be



	Initial HSRs			Total (N=58)	p
	Mild	Moderate	Severe		
BTRs					0.210
No reaction	5	10	17	32	
Mild	2	2	7	11	
Moderate	0	1	11	12	
Severe	0	0	3	3	

* Spearman correlation coefficient between initial HSRs and BTRs "Rho" = 0.350 ($p=0.02$)

Figure 3. The relationship between initial hypersensitivity reactions (HSRs) and breakthrough reactions (BTRs).

performed on every patient before administration of the 8th dose.²³ However, no research or established guidelines confirmed that proactive skin tests are useful in predicting HSR in patients exposed several times to chemotherapeutic agents; therefore, further prospective studies are needed.

It is known that RDD improves outcomes in patients with limited drug selection because of severe HSRs, but the mechanisms of desensitization are still incompletely understood, despite the various hypotheses that have been suggested. Sancho-Serra et al,³¹ using mouse bone marrow-derived mast cells, showed that internalization of a cell-surface immunoglobulin, the antigen/IgE/FcεRI complex, inhibited mast cell response in desensitization.³¹ Kepley³² and MacGlashan³³ showed that RDD impairs mast cell activation via depletion of activation-signal transduction components, such as syk kinase, and subthreshold depletion of mediators.^{32,33} The number of previous chemotherapy exposure-related BTRs may be associated with a greater number of IgE-expressing mast cells; more studies are required to validate the risk factors of BTRs and identify this mechanism.

Many studies have been conducted to modify desensitization protocols for reduced time and improved safety. In 2011, Gastaminza et al³⁴ reported shortening of the protocol, and Hong et al³⁵ proposed 1 solution in 2012, namely the 5-step protocol for cetuximab desensitization.³⁵ In 2018, Perez-Rodriguez et al³⁶

Table 5
Predictors of BTR during RDD after Multivariate Analysis

	OR	95% CI	P
BTR positive			
No. of previous cycle	1.12	1.00-1.25	.047
Severity of initial HSR	3.41	1.29-9.01	.014
Moderate to severe BTR			
History of drug allergy	7.83	1.48-41.44	.016
No. of previous cycle	1.14	1.01-1.28	.035
Severity of initial HSR	17.94	1.78-181.68	.015

BTR, breakthrough reaction; HSR, hypersensitivity reaction; RDD, rapid drug desensitization.

showed the safety of 1 rapid solution protocol of 490 desensitization in 90 patients.³⁶ In the current study, the average time for desensitization was more than 7 hours; thus, the patients needed hospitalization because preparation of the desensitization solution has difficult steps and takes time. After safety validation of these new rapid protocols, patient-specific desensitization protocols may be applied, which would be helpful to reduce the time needed and consequently increase the availability of the protocols for outpatient-based desensitization in clinics.

There are several limitations to this study. First, it was a retrospective analysis in a single hospital; thus, the sample size and data were insufficient to determine the risk factors of BTRs during the desensitization procedure. For instance, atopy status had also been investigated, but, owing to numerous missing values, the data were inadequate for analyzing logistic regression. Second, because skin tests were not conducted in all patients because of constraints in the administrative processes within the hospital, determining the relationship between positive skin test results and BTRs was difficult. Third, selection bias was unavoidable because of the large number of female patients and platinum desensitization procedures. Moreover, the target drug classes varied, suggesting that the mechanism of hypersensitivity and efficacy of desensitization may vary; however, the limited number of patients did not allow for subgroup analysis. Therefore, a prospective multicenter study involving proactive skin tests in high-risk patients is needed to verify the clinical significance of the risk factors found in this study, especially based on drug classes, to understand the underlying mechanism. Despite these limitations, this study provided relevant information regarding risk factors of moderate-to-severe BTRs, which is clinically important in real-world practice.

In this retrospective analysis using 3-year data from a single university hospital, a standardized 3-bag 12-step protocol for RDD was found to be effective and safe for most patients. However, considering the substantial time required for the desensitization procedure, hospital costs, and medical staff requirements, risk assessment for BTRs should be carried out before the start of desensitization. The desensitization protocols can be modified according to drug exposure history, drug allergy history, and severity of initial HSRs, which also can be used to predict high-risk patients. However, further studies are needed to validate BTR risk factors and to establish guidelines for the management and prevention of BTRs. In addition, reducing the number of desensitization steps, and identifying the time to switch to conventional chemotherapy according to the characteristics and chemotherapy needs of each individual patient would be beneficial. An individualized strategy considering drug history and initial HSRs will be helpful to realize prompt, safe, and efficient RDDs.

Through this retrospective analysis, we identified severity of initial HSR, drug allergy history, and previous high exposure to chemotherapeutic agents as variables positively correlated with above-moderate-grade BTRs. Our findings can help improve RDD protocols based on the severity and characteristics of HSRs for safe and effective targeted chemotherapies. Further studies are needed to determine risk stratification for high-risk patients and to modify desensitization protocols for patient-specific individualized treatment.

Supplementary Data

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.jana.2019.05.007>.

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Supplementary Data

eTable 1

Example of a 3-Bag, 12-Step Protocol (Target Dose 500 mg)

Total dose		500 mg	Total volume (mL)		Concentration (mg/mL)	
Solution A		2.0 mg ^a	100		0.020	
Solution B		20 mg ^a	100		0.20	
Solution C		500 mg ^a	250		2.00	
Step	Solution	Rate (mL/h)	Time (min)	Volume infused per step (mL)	Administered dose (mg)	Cumulative dose (mg)
1	A	2	15	0.5	0.01	0.010
2	A	5	15	1.25	0.025	0.035
3	A	10	15	2.5	0.05	0.085
4	A	20	15	5	0.10	0.185
5	B	5	15	1.25	0.25	0.435
6	B	10	15	2.5	0.50	0.935
7	B	20	15	5	1.00	1.935
8	B	40	15	10	2.00	3.935
9	C	10	15	2.5	5.00	8.935
10	C	20	15	5	10.00	18.935
11	C	40	15	10	20.00	38.935
12	C	60	230.53	230.53	461.065	500.00
Total			395.53 = 6.59 hours	276.03		500.00

^aThe sum of the dose in Solutions A, B, and C equals 522 mg. Total dose infused is 500 mg.**eTable 2**Results of the Skin Test^a

	Negative (N = 8)	Positive (N = 8)	Equivocal (N = 2)
Drug class			
Platins, N (%)	7 (88)	7 (88)	2 (100)
Cisplatin	4 (50)	—	1 (50)
Carboplatin	2 (25)	5 (62)	—
Oxaliplatin	1 (12)	2 (25)	1 (50)
Biologics, N (%)	1 (12)	1 (12)	—
Cetuximab	—	1 (12)	—
Rituximab	1 (12)	—	—

^aSPT and IDT produced the same results in tested patients.