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Research Article

Experience With Rapid Drug Desensitisation With Chemotherapeutics; A Single-Centre Retrospective Study

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Abstract

Objectives: Our aim is to share our platinum salt-, taxane- and irinotecan-induced rapid drug desensitisation (RDD) experiences.

Methods: In our study, the demographic data, initial HSR grades, skin test results and RDD success rates of patients who underwent a 12-step RDD protocol, and their breakthrough reactions (BTR) observed during desensitisation were retrospectively examined.

Results: The mean age of 28 patients who underwent RDD (platinum=22, taxane=4, irinotecan=2) was 57 (40-72), and 53.6% of the patients were female. 87 RDD procedures (platinum=56, taxane=21, irinotecan=10) were performed in total. 32.1% of the initial HSRs were grade 3 and 60.7% were grade 2. In terms of skin test results, 17 patients in the platinum group showed positivity to skin test. Two patients with negative results had a positive result on graded challenge. One patient in the taxane group had a negative skin test result yet had a grade 3 HSR. BTRs were observed in 46.4% of our patients – but none were at grade 3 in severity. 5 patients were unable to successfully complete the RDD protocol.

Conclusion: 12-step protocol was proven safe and efficient in our experiences with RDD. Our RDD success rate was 94.3%.

Keywords: Breakthrough reactions, chemotherapy, drug allergy, hypersensitivity reaction, rapid drug desensitisation

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Drug hypersensitivity reactions (HSRs) are expected during chemotherapy (CT) treatment regimens. Repeated drugexposure and/or drug formulation factors are defined as risk factors for the occurrence of immediate-type HSRs. Giventhat such HSRs are mild in terms of severity, they can be partially resolved with the use of premedication and slow-infusion.But ifHSRsare moderate to severe in severity,or skin tests confirm an allergy tothe drug in question, the first option is to switch to another low toxicity drug with the same efficacy. In cases where this option is out of the question, a rapid drug desensitisation (RDD) procedure with the responsible CT agent is performed instead.[1-3]

RDD is a treatment method in which mast cells are desensitised by gradually and periodically increasing the infusion rate of the responsible drug starting from lower to higher doses.[4-5] Desensitisation procedures for IgE- or non-IgE-mediated drug allergies can be reliably performed on numerous drug groups (antibiotics, biologic agents, non-steroidal anti-inflammatory drugs, radiocontrast agents etc.) including CT agents.[6-12] Desensitisation to CT agents was first performed in the 1990s. HSRs, which are now more fre-

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quent due to an increase in CT agent usage, have increased the need for desensitisation procedures, and over the years, the 12-step desensitisation protocol with well-proven efficacy and safety was developed.[13-15]

With this study, we aim to demonstrate the efficacy and safety of our protocol and contribute to the existing literature by sharing our experiences with 12-step desensitisation performed using antineoplastic agents.

Methods

Our study was carried out retrospectively in collaboration with Adult Allergy/Immunology and Medical Oncology clinics of an advanced tertiary central hospital. Patients over the age of 18 who developed an immediate-type HSR to antineoplastic drugs and underwent a desensitisation procedure between September 2019 and February 2021 were included to this study. The evaluation of all patients, the decision of going through with an RDD procedure and the preparation of the RDD protocol were all made and carried out by an allergy specialist.

Patients

The age, sex, comorbidities, drug allergy histories and malignancy type of the patients, the name of the suspected drug they developed reactions to, the observed allergic symptoms and thesteps during whichthe allergic symptoms occurred were questioned. HSRs were categorized as grade 1 (mild) *[Symptoms are limited to the skin (e.g., flushing) or involve a single organ/system and are mild (e.g., mild back pain)]*, grade 2 (moderate) *[Symptoms involve at least 2 organs/systems (e.g., flushing and dyspnoea), but there is no significant decrease in blood pressure or oxygen saturation]* and grade 3 (severe) *[Severe symptoms typically involve at least 2 organs/systems, and there is a significant decrease in blood pressure (systolic<90 mm Hg and/or syncope) and/or oxygen saturation (<92%)]* according to Brown classification.[16] Skin tests were performed thereafter.

Skin tests were carried out according to the European Network for Drug Allergy/European Academy of Allergy and Clinical Immunology (ENDA/EAACI) recommendations.[17] The patients were required not to have used corticosteroid and antihistaminic drugs 7 days prior to the test. The skin tests were performed within 7 to 40 days and were personalized for each patient in a way that they do not interfere with their cancer treatment.

The suspected drugs were first tested with skin prick tests (SPT). Intradermal (ID) tests were performed on ones with negative SPT results afterwards. Drug concentrations for the SPT were carboplatin 10 mg/mL, cisplatin 1 mg/mL, oxaliplatin 5 mg/mL, paclitaxel 6 mg/mL, docetaxel 10 mg/mL. Drug concentrations for the ID test were carboplatin 1 mg/mL, cisplatin 0.1 mg/mL, oxaliplatin 0.5 mg/mL, paclitaxel 0.06 mg/mL, docetaxel 1 mg/mL.[15] A weal of 3 mm or more in diameter for SPTs or an increase in diameter of the initial ID of 3 mm or more were defined as a positive test, provided that the two conditions, a negative response to control solution (0.9% saline) and a positive response to histamine (SPT: 10 mg/mL) were satisfied.

For evaluating the atopies of the patients, an aeroallergen panel (Allergopharma, Stockholm, Sweden)widely utilized in skin tests was used.

The decision on which patients were to undergo desensitisation was based on their HSR grades and skin test results. The following patient groups have undergone desensitisation:

Patients who had a skin test:

- Patients who had a positive skin test result with the suspected drug
- Patients who had a negative skin test result with the suspected drug but had grade 3 HSR
- Patients whohad a negative skin test result with the suspected drug but had grade 1 to 2 HSR and therefore, underwent a gradual challenge with the suspected drug and showed positivity

Patients who did not have a skin test:

- All patients with grade 2 to 3 HSRs

Desensitisation Protocol

As part of the standard, 3 varied drug dilutions were made. Bag A was at 1:100, B at 1:10 and C at 1:1 of the parent drug,each in 250 mL volume with a 5% dextrose or 0.9% saline content. Infusion was initiated starting from the bag A,which was used in the steps 1 to 4, then bagB was used for the steps 5 to 8 and finally bagC for the steps 9 to 12. In this 12-step protocol, the plan was to reach the target drug dose in 5.82 hours by increasing the infusion rate at 15-minute (min) intervals. A 16-step protocol was developed for patients with near-fatal anaphylaxis by preparing an additional bagdiluted at 1:1000 ratio. Desensitisations were performed in a clinical setting under the personal supervision of a nurse and an oncology specialist so that immediate actions can be taken if and when the need arises. Patients were intravenously given methylprednisolone (kg/0.5 mg), antihistaminic (pheniramine 45.5 mg) and a H2 receptor blocker (ranitidine 50 mg) as premedication 30 minutes prior to the procedure. A patient's vital signs were recorded before and during the procedure for 30 minutes.[2, 18]

During desensitisation, the infusion would be shut each time HSRs occurred to treat patients' symptoms. Once the

symptoms were treated and restrained, the infusion would resume from the previous step. But in cases where patients experienced a grade 3 HSR, the procedure would discontinue.

Statistical Analysis

We used SPSS (version: 22.0Armonk NY, IBM Corp. 2013) for statistical analysis. For descriptive analysis, we presented continuous variables as mean with standard deviation (SD) or as median with quarter range (IQR) as suitable. The numerical variables between two independent conditions were analysed by Student-t test in case of normal distribution and by Mann-Whitney-u test in case of the opposite.

Results

Skin tests were performed on all but 6 of the 115 patients who have been reported to have an immediate-type HSR during chemotherapy treatment regimen in the last 1.5 years. After the evaluations, 28 patient who underwent an RDD were included to the study. The median age was 57 (40-72) and 53.6% of the patients were female. 35.7% of the patients had ovary cancer, 25% lung cancer, 21.4% colorectal cancer, 7.1% breast cancer, 7.1% pancreatic cancer, 3.6% gastric cancer and 67.9% of the patients had their disease in the metastatic stage. 35.7% of the patients had comorbidities (hypertension, diabetes mellitus, asthma, coronary artery disease etc.), 3.5% had atopy, 14.3% had drug allergy history. Platins were the main culprit drugs in our study group, followed by paclitaxel. Distribution of desensitised drugs is as follows: carboplatin (n=12), oxaliplatin (n=8), cisplatin (n=2), paclitaxel (n=4) and irinotecan (n=2). Demographic and clinical characteristics of patients are presented in Table 1.

Skin Test Results and Desensitisation Decisions

In the platinum group, 19 out of 22 patients were tested with the skin test and 17 of them had a positive result: carboplatin (n=10; IDT [n = 5], prick [n=5]), oxaliplatin (n=5; IDT [n=4], prick [n=1]) and cisplatin (n=2; both IDT). Two patients from the platinum group who had negative skin test results underwent desensitisation regardless,since their graded drug provocation test results were positive.Direct desensitisation was applied to the 3 patients who were unable to undergo skin testing.

A skin test with paclitaxel was performed on one patient and found negative. Desensitisation was applied to this patient due to a grade 3 HSR. Direct desensitisation was applied to other 3 patients who could notundergo skin testing.

No skin test with irinotecan was performed due to a lack of knowledge regarding its irritative dose. Direct desensitisation was applied to patients with grade 2 HSR (Table 1).

Characteristics of Initial HSRs

Three carboplatin users (13.6%) and 1 paclitaxel user (25%) developed HSRs after initial drug exposure. The remaining patients developed HSRs after repeated drug exposures. We have found that drug-induced HSRs developed at an average drug exposure of 6.37±5.1 in the platinum group and 2.50±1.0 in the taxane group. 32.1% of HSRs were grade 3, 60.7% were grade 2. None of our patients with grade 3 HSRs experienced cardiac and/or respiratory arrest. Initial reaction grades and cycles of all patients are presented in Table 1.

The most common platinum drug-related reactions were cutaneous (77.3%), while paclitaxel drug-related ones were mostly consisted of respiratory symptoms (%100). A detailed distribution of the observed symptoms associated with the drugs are presented in Table 2.

Rapid Drug Desensitisation

A total of 87 RDDs were performed on 28 patients. As for the distribution of the patients who underwent RDDs: 56 RDDs were performed with platinum drugs (carboplatin n=27, 31.0% of RDDs; oxaliplatin n=25, 28.7% of RDDs; cisplatin n=4, 4.6% of RDDs) and a total of 21 RDDs were performed on 4 paclitaxel users (24.1% of RDDs). 10 RDDs were performed on 2 irinotecan users (11.5% of RDDs) (Fig. 1). A 4-bag protocol was applied to one of our patients due to occurrence of HSRsin the first couple minutes of the procedure. Such HSRs included urticaria, abdominal pain, syncope and continued in the form of hypotension.All desensitisation procedures were carried out in a clinical setting under personal supervision of a nurse.

15 of the 28 patients who underwent RDDs were able to take their medications without experiencing any allergic reactions. 13 patients developed a breakthrough reaction (BTR) and 5 of these patients' RDD procedure was discontinued. In 8 patients, desensitisation procedure was successfully completed with steroid and/or antihistaminic treatments. Grade 2 reactions were observed in 3 out of the 5 patients who had to discontinuethe desensitisation procedure. The remaining two patients showed grade 1 reactions (Table 3). Out of these 5 patients who had to discontinue the procedure, 2 had to cancel due topersistent grade 2 BTRs which continued despite returning to the previous steps in infusion. The remaining 3 patients had to undergo their RDDs without the supervision of an oncology doctor and their desensitisations had to be terminated upon the occurrence of an allergic reaction without resorting to dose adjustments. In total, 94.3% of the 87 RDD protocols were successful and 5.7% were failed.

Table 1. Demographic and clinical characteristics of the study group

Case No/Name	Sex	Age, years	Comorbidity	Primary Malignancy	Atopy	History of drug allergy	Chemoteraphy	Skin tests	HSR		Number of RDDs	Rx Grade
									Cycle	Grade		
1 (CA)	M	60	HT	Lung	Neg.	No	Carboplatin	Prick (+)	13	III	2	I
2 (HA)	M	66	----	Colorectal	Neg	No	Oxoloplatin	IDT (+)	3	III	2	I
3 (NT)	F	72	----	Ovary	Neg	No	Carboplatin	Prick (+)	6	II	3	0
4 (SD)	M	44	----	Lung	Neg	Yes	Carboplatin	IDT (+)	1	I	1	0
5 (MK)	M	62	----	Colorectal	Neg	No	Oxoloplatin	IDT (+)	9	II	1	0
6 (MS)	F	46	----	Pancreatic	Neg	No	Irinotecan	ND	2	II	1	I
7 (İD)	F	53	DM	Gastric	Neg	No	Oxoloplatin	Neg	3	II	1	0
8 (NK)	F	55	COPD, HT,DM	Ovary	Neg	No	Carboplatin	Prick (+)	6	III	5	II
9 (SA)	F	51	----	Ovary	Neg	No	Carboplatin	IDT (+)	9	II	2	0
10(SO)*	F	45	----	Ovary	Neg.	No	Carboplatin	IDT (+)	10	III	1	0
11 (HO)	M	58	CAD	Lung	Neg	No	Cisplatin	IDT (+)	5	I	1	I
12 (NT)	M	57	----	Colorectal	Neg	No	Oxoloplatin	ND	2	II	3	0
13 (NS)	M	51	----	Lung	Neg	No	Paclitaxel	ND	1	II	4	0
14 (TÖ)	M	70	COPD, HT	Lung	Neg	Yes	Carboplatin	IDT (+)	1	II	2	I
15 (MA)	M	62	DM, HT	Lung	Neg	No	Oxoloplatin	Prick (+)	13	III	6	I
16 (OT)	M	40	----	Colorectal	Neg	No	Oxoloplatin	Prick (+)	2	II	1	II
17 (ŞT)	F	57	----	Colorectal	Neg	No	Oxoloplatin	ND	9	III	4	I
18 (HÇ)	F	70	----	Ovary	Neg	No	Carboplatin	Prick (+)	3	II	1	I
19 (SC)	F	60	----	Breast	Neg.	No	Paclitaxel	ND	3	II	9	0
20 (AD)	F	56	----	Breast	Neg	No	Paclitaxel	ND	3	II	5	0
21 (AÇ)	F	56	DM	Ovary	Neg	No	Cisplatin	IDT (+)	4	II	3	0
22 (SE)	F	66	DM	Ovary	Neg	Yes	Carboplatin	ND	16	III	3	0
23 (GM)	F	56	DM	Ovary	Neg	No	Carboplatin	Neg	18	II	5	0
24 (FT)	M	70	----	Lung	pollen	Yes	Paclitaxel	Neg	3	III	3	0
25 (SA)	F	70	CAD	Pancreatic	Neg	No	Irinotecan	ND	2	II	9	I
26 (FB)	M	57	----	Colorectal	Neg	No	Oxoloplatin	IDT (+)	3	II	7	0
27 (SA)	M	65	----	Ovary	Neg	No	Carboplatin	IDT (+)	1	II	1	II
28 (HK)	F	51	----	Ovary	Neg	No	Carboplatin	Prick (+)	3	III	1	II

HSR: hypersensitivity reaction; Rx: breakthrough reactions; RDD: rapid drug desensitization; Neg: negative; IDT: intradermal test; HT: hypertension; DM: diabetes mellitus; COPD: chronic obstructive pulmonary disease; CAD: coronary artery disease; ND: not done. * A 4-bag protocol was performed.

Table 2. Symptoms and signs during initial HSRs in 28 patients

	Carboplatin (n=12)	Oxaloplatin (n=8)	Cisplatin (n=2)	Paclitaxel (n=4)	Irinotecan (n=2)
Symptoms and signs, n (%)					
Cutaneous	9 (75.0)	6 (75.0)	2 (100)	2 (50.0)	2 (100)
Flushing*	3 (25.0)	1 (12.5)	1 (50.0)	2 (50)	0 (0)
Pruritus	3 (25.0)	2 (25.0)	2 (100)	0 (0)	0 (0)
Urticaria	6 (50.0)	4 (50.0)	2 (50.0)	0 (0)	0 (0)
Angioedema	1 (8.3)	0 (0)	0 (0)	0 (0)	2 (100)
Cardiovascular	7 (58.3)	4 (50.0)	0 (0)	3 (75.0)	0 (0)
Chest pain	1 (8.3)	0 (0)	0 (0)	3 (75.0)	0 (0)
Presyncope	2 (16.7)	1 (12.5)	0 (0)	0 (0)	0 (0)
Syncope	2 (16.7)	2 (25.0)	0 (0)	1 (25.0)	0 (0)
Hypotension	2 (16.7)	3 (37.5)	0 (0)	1 (25.0)	0 (0)
Palpitation	2 (16.7)	0 (0)	0 (0)	0 (0)	0 (0)
Respiratory	8 (66.7)	2 (25.0)	1 (50.0)	4 (100)	2 (100)
Dyspnea	8 (66.7)	2 (25.0)	1 (50.0)	4 (100)	1 (50.0)
Desaturation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Throat tightness	1 (8.3)	0 (0)	0 (0)	0 (0)	1 (50.0)
Gastrointestinal	1 (8.3)	4 (50)	0 (0)	1 (25.0)	1 (50.0)
Nausea/vomiting	1 (8.3)	3 (37.5)	0 (0)	0 (0)	0 (0)
Abdominal pain	0 (0)	1 (12.5)	0 (0)	1 (25.0)	1 (50.0)

HSR: hypersensitivity reaction; *Defined as erythema, warmth, or both.

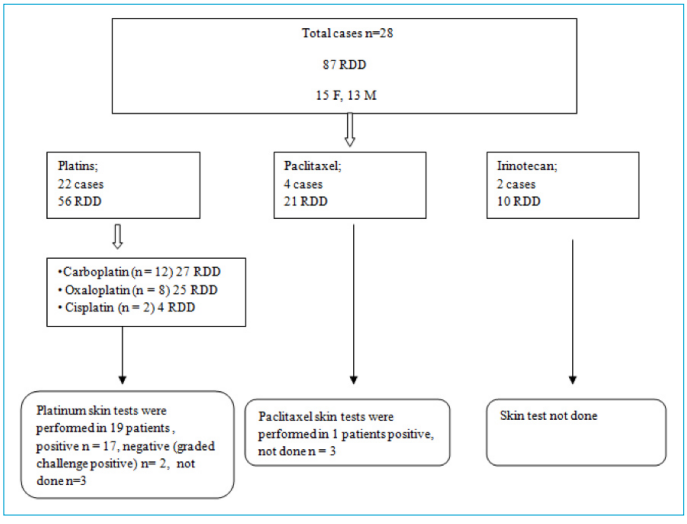

Figure 1. The number of patients who reacted individual chemotherapeutics and total number of RDDs for each chemotherapeutic.

Breakthrough Reactions

BTRs were seen in 13 out of 28 patients who underwent an RDD and in 17 out of 87 RDD protocols.In 9 of these 13 patients (69.2%), BTRs occurred during the first desensitisation procedure, while in 2 patients, the reactions were seen during the 2nd and 3rd desensitisation procedures. One patient developed BTRs during all 5 desensitisation procedures. 88.2% of the BTRs developed while using bag C (70.6%) at the 12th step.69.2 percent of the reactions were grade 2 and 30.8% were grade 1. No grade 3 reactions were observed in any patient. In the paclitaxel group, none of the patients experienced BTRs. No BTR was observed in the patient who underwent a 4-bag protocol as well. The observed symptoms are presented in Table 3. No intensive care need or mortality due to BTRs was observed in any patients.

Discussion

In this study, safety and efficacy of 12-step RDD with antineoplastic agents performed in the last 1.5 years were retrospectively examined. 87 RDD protocols with platinum salts, taxanes and irinotecan drugs were applied to 28 patients and 94.3% of these protocols were successfully completed. On a patient basis, 23 (82.1%) out of 28 patients had successfully completed their RDD protocols. Thanks to drug desensitisation method, the vast majority of the patients were able to continue taking the necessary active drugs for their cancer treatments.

In the last few decades, various desensitisation protocols have been performed for chemotherapeutic agents. Such protocols may use different numbers of bagsand steps and can change in duration(e.g., the 2-hour RDD protocol performed on 11 female patients by Gastaminza A et al., single-bag protocol performed on 90 patients by Pérez-Rodríguez E et al.).[19-20] Pérez-Rodríguez E et al. found a soaring success rate of 94.69% for 490 RDD procedures.

Table 3. Details of the breakthrough reactions (Rx)

Case No	Name	Age, years	Primary Malignancy	Atopy	Chemoteraphy	Skin tests	HSR Grade initial	RDD, N	Breakthrough Rx	Rx Grade	Completed
1	CA	60	Lung	Neg.	Carboplatin	Prick (+)	III	2	1st RDD, 12th step (C) flushing, erythema	I	Yes
2	HA	66	Colorectal	Neg	Oxoloplatin	IDT (+)	III	2	2nd RDD, 12th step (C) flushing	I	Yes
3	MS	46	Pancreatic	Neg	Irinotecan	ND	II	1	1st RDD, 5th step (B) angioedema	I	No
4	NK	55	Ovary	Neg	Carboplatin	Prick (+)	III	5	1,3 RDD, 9th step(C) 2,4,5 RDD, 12th step (C) flushing, itching, chest pain and dispne	II	Yes
5	HO	58	Lung	Neg	Cisplatin	IDT (+)	I	1	1st RDD, 3th step(A) dispne	I	Yes
6	TÖ	70	Lung	Neg	Carboplatin	IDT (+)	II	2	2nd RDD, 12th step(C) flushing	I	Yes
7	MA	62	Lung	Neg	Oxoloplatin	Prick (+)	III	6	3nd RDD, 11th step(C) flushing, itching	I	Yes
8	OT	40	Colorectal	Neg	Oxoloplatin	Prick (+)	II	1	1st RDD, 12th step(C) flushing, itching and dispne	II	No
9	ŞT	57	Colorectal	Neg	Oxoloplatin	ND	III	4	1st RDD, 12th step(C) flushing, itching	I	Yes
10	HÇ	70	Ovary	Neg	Carboplatin	Prick (+)	II	1	1st RDD, 12th step(C) flushing, itching	I	No
11	SA	70	Pancreatic	Neg	Irinotecan	ND	II	9	3nd RDD, 12th step(C) angioedema	I	Yes
12	SA	65	Ovary	Neg	Carboplatin	IDT (+)	II	1	1st RDD, 12th step(C) flushing, itching and nausea	II	No
13	HK	51	Ovary	Neg	Carboplatin	Prick (+)	III	1	1st RDD, 12th step(C) flushing, itching and dispne	II	No

HSR: hypersensitivity reaction; Rx: breakthrough reactions; RDD: rapid drug desensitization; Neg: negative; IDT: intradermal test; ND: not done.

In their study however, although the success rate of the single-bag protocol was high in the non-platinum group agents, the same efficacy was not present in the platinum group. Also, BTRs requiring epinephrine injections were observedduring the RDDs of the platinum group patients. Considering these results, it can be concluded that this protocol lacks the sufficient safety and efficacy for the platinum group drugs.[20] The 12-step RDD protocol developed at Brigham and Women's Hospital (BWH) is considered as the safest and most effective desensitisation protocol.[2, 14, 15] Hence, we preferred using this 12-step protocol which is well-proven in terms of safety and efficacy.No BTRs requiring an epinephrine injection were observed during the RDDs of our patients. The majority of our patients were users of platinum group agents and our RDD had 94.3% success rate. Kendirlinan et al. who performed the same protocol found a success rate of 98.3% in 41 patients over 122 RDD procedures.[21] The reason why our success rate is lower is the lack of personal supervision due to having only one allergy specialist in the hospital which led to lack of dose modifications during reactions. This is reflected on three out of 5 unsuccessful cases where the procedure was put on hold to treat allergic symptoms of the patients upon BTR occurrence and the RDDs were cancelled without returning back to previous steps. This, indeed, understates our true success rate. In reality, RDD was discontinued in only 2 of our patients due to persistent allergic reactions despite returning to previous steps and adjusting doses upon BTR occurrence.

In our study, RDDs were performed with platinum salts, taxanes and irinotecansince allour patients showed negative results on skin testsforHSRs to biologic agents (trastuzumab, pertuzumab, cetuximab and panitumumab) and had grade 1-2 HSRs. HSRs of

all of these patients were resolved with premedication and slow-infusion, thus negating the need for RDDs. Thus, unnecessary RDD protocols were avoided. For this reason, the data shared in this study solely relates to RDD protocols with platinum salts, taxanes and irinotecan.

It has been reported in many studies to this date that initial HSRs occur averagely after 6 to 10 drug exposuresfor platinum group agents, and 2 for taxanes.[22, 23] In line with our data, HSRs were observedat an average drug exposure of 6.37±5.1 for the platinum group and 2.50±1.0 for the taxane group.13 out of 28 patients (46.4%) who underwent RDD developed BTRs. Similarly, Kang Y et al. also found the BTR rate to be 45% in their recent study.[24] Although BTR was observed in almost half of the patients, none of them were at grade 3 in terms of severity. As another point to consider,most of our patients completed their RDD procedures despite BTR reactions. Similarly, high success rates can also be seen in other studies despite high BTR occurrence rates, such as 39%, in 12-step RDD protocols.[2, 21]

The data we have obtained during our study show that the 12-step RDD protocol is effective and safe for patients. It can be concluded that RDD success ratescan be raised if they are performed under the personal supervision of an allergy specialist.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital with approval number of 514/188/12. (27.10.2020).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.A.; Design – M.A., K.T.; Supervision – K.T.; Materials – M.A., K.T.; Data collection &/or processing – M.A., K.T.; Analysis and/or interpretation – M.A.; Literature search – M.A., K.T.; Writing – M.A., K.T.; Critical review – M.A., K.T.

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