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Rapid drug desensitization with chemotherapy: when should omalizumab be considered?

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Abstract
Background: All chemotherapy agents have the potential risk of developing hypersensitivity reactions (HSRs). In patients who develop HSRs, rapid drug desensitization (RDD) enables the use of a treatment option that prevents disease progression. If RDD fails to elicit the desired results or in patients with baseline HSRs Brown grades 2-3, omalizumab may also be a treatment option. Our primary aim is to share the demographic and clinical characteristics of our patients who underwent RDD. Our secondary aim is to share our experience with omalizumab during RDD in difficult cases.
Methods: This was a retrospective study of patients with immediate-HSRs to chemotherapeutic (CHT) agents. Initial HSRs were classified as grades 1, 2, or 3 based on severity. Prick/intradermal skin tests were performed with implicated agents. In grade 3 reactions and skin prick test (SPT)-positive patients, a 16-step desensitization was applied. A 12-step desensitization was applied in other patients. In 10 patients, omalizumab was administered for premedication.
Results: The study analyzed data from 80 patients (F/M: 60/20). The number of patients who received different medictions was as follows: carboplatin-23, paclitaxel-22, oxaliplatin-21, dasotaxel-9, etoposide-1, docorubicin-1, pertuzimab-1, paclitaxel+herceptin-1, and bevacizumab+oxaliplatin-1. Inıtıal HSRs were grade 1: 27(%33,7) , grade 2: 30 (%37,5), and grade 3: 23(% 28,7). A total of 22 patients (27.5 %) had atopy based on SPT. Skin tests with implicated agents were done on 78 patients. For the inıtıal HSR grades 1, 2, and 3, the number of positive skin test responses was 25/27, 27/29, and 17/22, respectively. A total of 377 RDDs were performed completely, but 22 patients developed 3 reactions during RDD (grade 1: 77.2%, grade 2: 13.6%, and grade 3 9%). All patients received a mean of 4.7 (minimum: 1, maximum: 23) RDDs. There was no statistical difference in the severity of reaction, system involvement, and distribution of symptoms between platinum and taxanes groups. The rate of reaction during RDD was higher in patients receiving platinum compared with taxan. Ten patients

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received omalizumab before RDD. Initial HSRs were grade 3 in 8 patients; the responsible agent was platinum in 5 patients; and 1 patient developed grade 3 HSR during RDD. In four patients, ınıtıal HSRs were grades 2 and 3, and desensitization was not continued when HSR developed during RDD. A total of 373 successful RDDs were performed.
Conclusions: RDD is a very important treatment applied to patients with immediate-HSRs to CHT agents. Omalizumab facilitated the continuation of chemotherapy in patients with index reaction grades 2–3. It provided an opportunity for 8 of 10 patients with Grade 2–3 severe reactions to continue treatment. In our population, 98.9% (373/377) successful completion of RDDs in all chemotherapy groups demonstrates the safety of this procedure.

Introductıon

Chemotherapy is a long-standing treatment option in cancer patients. It is administered to 28% of patients diagnosed with cancer,[1] and hypersensitivity reaction (HSR) develops in 5% of patients receiving chemotherapy.[2,3] When hypersensitivity develops, the prominent treatment option is rapid drug desensitization (RDD). RDD is the most effective, usually less costly, first-line treatment option to patients.[4] It is an effective treatment option that has been shown to be successful in large patient cohorts. However, even many allergy clinics find the RDD procedure to be risky. Treatment management in patients with severe inflammatory reactions is challenging for specialists. Despite the 12-step RDD, the 16-step RDD in symptomatic patients led to less development of HSR.[5] In the literature, data on the use of omalizumab before RDD are based on case reports.[6–9]

To date, we have performed 373 RDDs in 80 patients. We aim to describe the characteristics of our patients with chemotherapy hypersensitivity and the results of RDD. Our second aim is to share our experience with omalizumab, which we used in patients with severe initial reaction or hypersensitivity during RDD. This study has the highest number of patients in the literature in terms of the use of omalizumab before RDD. In this way, we thought that we could help physicians more in the management of difficult patients.

Methods

Study design

This study was conducted in the Department of Allergy Immunology at Health Sciences University, Süreyyapaşa Chest Diseases and Thoracic Surgery Training and Research Hospital and retrospectively designed (2015–2023). Approval from the Ethics Committee was obtained prior to the study (116.2017.R-341). In addition, approval was obtained from the Ministry of Health to publish the data because of the off-label use of omalizumab (E-24931227-506.01-5591579). All patients were older than 18, and written informed consent was obtained. We have previously performed RDD with the same protocol and the data of 51 patients were also mentioned in our previous study.[10]

Study population

Patients who developed hypersensitivity because of exposue to chemotherapy agents underwent RDD. Patients were assessed with regard to demographic data, gender, and age; comorbid diseases, diagnosis of malignancy; severity of reaction and systems involved; skin prick test (SPT)/ intradermal test for diagnosis, eosinophil counts, and serum tryptase levels; agent applied during RDD/number of RDDs/ development of hypersensitivity during the RDD process; use of omalizumab for premedication; and characteristics of patients who received omalizumab.

Rapid drug desensitization

Patients underwent a 12-step, 3 dilution RDD. If the skin test was positive or if the immediate reaction was that of cardiac arrest, some patients underwent a 16-step, 4 dilution RDD. In some patients who developed grades 2–3 HSR or whose immediate reaction was grade 3 cardiac arrest during RDD, omalizumab was administered for premedication after obtaining off-label approval from the Ministry of Health. RDD was performed under nurse supervision. Written informed consent was obtained from the patients. If the prick test with chemotherapeutic (CHT) drugs was negative, especially with taxanes, premedication was administered. We used montelukast, cetirizine, and methylprednisolone for premedication.

Omalizumab

As of now, omalizumab is not licensed for RDD.[11] However, it has been proposed in studies involving a small number of patients. Differences in dose and timing of administration are noteworthy.[9,11] We decided the dose of omalizumab and timing according to the patient's initial HSR and chemotherapy cycle.

Statistical analysis

The data from the study were analyzed with SPSS (Statistical Package for Social Sciences) 22.0 package

program. In descriptive analyses, frequency data were given as number (n) and percentage (%) and numerical data were given as arithmetic mean±standard. Pearson Chi-square and Fisher's Exact test were used to compare categorical data. The conformity of the numerical data to normal distribution was evaluated with sample size, histogram, and Q-Q plot graphs. The distribution of normally distributed numerical data in two independent groups was analyzed by Independent Groups T-test. The level of statistical significance was $p<0.05$ for all tests.

Results

Demographics and clinical features of patients

In the study, data from 80 patients (60 women and 20 men) were analyzed. The demographic and clinical characteristics according to the CHT agent are detailed in Table 1. The severity of HSRs to CHT agent as per Brown's symptoms according to the systems and desensitization process are detailed in Table 2. Twenty-two patients (27.5 %) had atopy based on SPT. Eleven had rhinitis, eight had asthma, and one had mastocytosis. The diagnoses were ovarian cancer (n: 25, 31.2%), breast cancer (n: 22, 27.5%), colorectal cancer (n: 20, 25%), stomach cancer (n: 4, 5%), lung cancer (n: 4, 5%), endometrium cancer (n: 3, 3.75%), and prostate cancer (n: 2, 2.5%). Among all CHTs, carboplatin and paclitaxel were most frequently responsible for HSRs. For carboplatin, HSRs developed at a mean of 9.9 infusions; for paclitaxel, HSRs developed at a mean of 4 infusions.

Table 3 provides a comparison of patients who received omalizumab before RDD with other patients. There was no statistical difference between the two groups in terms of age and gender ($p>0.05$). Smoking was significantly higher in patients who received omalizumab before RDD ($p=0.018$). In the omalizumab group, three patients had allergic disease; the most common malignancy was ovarian cancer in six patients; 80% of patients were in stage 4 metastatic stage; atopy was present in 40% patients.

There was no statistically significant difference in the distribution of laboratory measurements between the omalizumab-treated group and the other group ($p>0.05$) (Table 4).

RDD was performed with platinum agents in 45 patients and with taxan in 32 patients. The characteristics of allergic reactions and RDD procedures in platinum and taxan groups are compared in Table 5. The dose of reaction development in the platinum group was significantly higher than the taxan group ($p=0.003$). There was no statistical difference in the severity of reaction, system involvement, and distribution of symptoms between platinum and taxan groups ($p>0.05$). The rate of reaction during RDD was higher in patients receiving platinum compared with those receiving taxan ($p<0.001$). When HSRs developed, the cumulative chemotherapy dose was higher in patients receiving platinum than taxanes; the number of RDDs administered after the development of HSRs was lower in the platinum group (p values: $p<0.001$; $p=0.002$).

The details of patients who received omalizumab before RDD are given in Table 6.

Discussion

In this retrospective study, RDD data, which were successfully applied to 80 patients with a rate of 98.9% (373/377), were shared. Omalizumab was administered before RDD in 10 patients who developed Brown grades 2–3 or breakthrough reactions (BTRs) during RDD. This study is the largest series on the administration of omalizumab before the administration of the CHT agent, RDD.

Over the years, many CHT agents have been employed in the treatment of cancer. Platines were the most common drugs involved in HSR (45%), followed by taxanes (34%) and biological therapies (18%).[12] According to the current literature, the group most frequently responsible for HSR is platines and among them carboplatin.[2,13] In our study, the most responsible agent for HSR is carboplatin (n: 23, 28.7%), followed by paclitaxel (n: 22, 27.5%). Carboplatin allergy may also increase with continuing exposure beyond eight cycles.[14] Studies have shown that an average of 12% of patients receiving eight or more carboplatin infusions over a lifetime will develop a HSR to this drug with a positive skin test, meaning that this is an acquired hypersensitivity resulting from sensitization.[15-17] In our study, on average, the reaction with platins developed in the eigth cycle and with taxanes in the fourth cycle. This reached statistical significance ($p = 0.003$). In a study conducted in Turkiye. HSR with taxanes was observed in the first two cycles.[18,19] In our study, it developed in the fourth cycle on average.

Most of the patients were female (75%), with many patients having breast, over, and endometrial cancers. Platins and taxanes are used in the treatment of many cancers, most of them being colorectal, breast, over, prostate, and gynecologic cancers.[19,20] In our study, the most prevalent diagnosis was over cancer (n: 25, %31.2), followed by breast (n: 22, % 27,5) and colorectal cancer (n: 20, %25).

All of our patients had stages 3–4 advanced disease; 70 (87.5%) patients had stage 4 advanced disease. Chemotherapy is a treatment modality, especially for advanced disease.

Twenty-three (87.5%) patients had atopy, that is, a positive skin prick test with respiratory allergens. There was no significant difference between chemotherapy agents and atopy percentages, and there was no statistical significance between patients treated with omalizumab and other patients in terms of atopy. A history of atopy was calculated as 27.2% in the study by Alen et al.[21]

Skin prick and intradermal test positivity with CTH was higher in the platinum group than in the taxan group, but it did not reach statistical significance. Skin prick or intradermal test positivity was seen in 48.8% (n:22) with platinum and 31.2% (n:10) with taxanes. Skin test positivity is important in determining risk before desensitization. HSRs developed in 86% of patients positive for skin test with standard infusion.[16] There are successful results with step-down and infusion rate reduction in patients with negative skin tests.[22] Although we have no experience with step down for taxanes, the number of steps was reduced to eight in one patient receiving platinum because HSR did not develop during multiple RDDs.

The most commonly used classifications include the Brown's grading system.[22,23] Regarding the severity, 37.5% (n = 30) of the reactions were grade 2, 27% (n = 33.7) were

Table 1 Demographic and clinical characteristics of patients according to chemotherapeutic agents.

	Carboplatin (n=23)	Paclitaxel (n=22)	Oxaliplatin (n=21)	Docetaxel (n=9)	Etoposide (n=1)	Doxorubicin (n=1)	Pertuzimab (n=1)	Paclitaxel+ Herceptin (n=1)	Bevacizumab+ Oxaliplatin (n=1)
Age (years)	57.26±10.84	53.86±12.52	56.38±13.77	49.44±11.3	60	55	61	47	73
Female, n (%)	21 (91.3)	19 (86.4)	8 (38.1)	7 (77.8)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
Cigarette smoking (%)	11 (47.8)	11 (50)	11 (52.4)	4 (44.4)	1 (100)	-	-	-	1 (100)
Cigarettes (packets/year)	41.8±15	28±18.9	32.9±12.8	28.7±7.5	60	-	-	-	55
Hypertension, n (%)	8 (34.8)	7 (31.8)	6 (28.6)	3 (33.3)	-	-	-	-	1 (100)
Allergic Disease, n (%)									
No	17 (73.9)	17 (77.3)	-	8 (88.9)	1 (100)	-	1 (100)	1 (100)	1 (100)
Rhinitis	4 (17.4)	3 (13.6)	4 (19.0)	-	-	-	-	-	-
Asthma	2 (8.7)	2 (9.1)	3 (14.3)	1 (11.1)	-	-	-	-	-
Mastocytosis	-	-	-	-	-	1 (100)	-	-	-
Diagnosis, n (%)									
Colorectal cancer	-	1 (4.5)	18 (85.7)	-	-	-	-	-	1 (100)
Ovarian	16 (69.6)	9 (40.9)	-	-	-	-	-	-	-
Stomach	-	1 (4.5)	3 (14.3)	-	-	-	-	-	-
Breast	3 (13)	9 (40.9)	-	7 (77.8)	-	1 (100)	1 (100)	1 (100)	-
Lung	2 (8.7)	1 (4.5)	-	-	1 (100)	-	-	-	-
Endometrial	2 (8.7)	1 (4.5)	-	-	-	-	-	-	-
Prostate	-	-	-	2 (22.2)					
Cancer Stage, n (%)									
Stage 3	1 (4.3)	4 (18.2)	4 (19)	1 (11.1)	-	-	-	-	-
Stage 4	22 (95.7)	18 (81.2)	17 (81)	8 (88.9)	1 (100)	1 (100)	1 (100)	1 (100)	1(100)
Death, n (%)	9 (39.1)	6 (27.3)	13 (61.9)	1 (11.1)	1 (100)	-	-	-	1 (100)
Atopy, n (%)	6 (26.1)	5 (22.7)	8 (38.1)	3 (33.3)	-	1(100)	-	-	-
Other drug HSRs, n (%)	-	4 (18.2)	1 (4.9)	-	-	1 (100)	-	-	-

Mean±SD, n(%).
HSRs: Hypersensitivity reactions.

Table 2 The severity of HSRs to chemotherapeutic agent according to Brown's symptoms and desensitization.

	Carboplatin (n=23)	Paclitaxel (n=22)	Oxaliplatin (n=21)	Docetaxel (n=9)	Etoposide (n=1)	Doxorubicin (n=1)	Pertuzimab (n=1)	Paclitaxel+ Herceptin (n=1)	Bevacizumab+ Oxaliplatin (n=1)
HSR developing cycles	9.9±3.5	4±7.5	6.4±4.35	1.7±0.5	2	1	4	5	3
Severity of HSR (Brown)									
Grade 1	5 (21.7)	9 (40.9)	8 (38.1)	3 (33.3)	-	-	-	1 (100)	1(100)
Grade 2	10 (43.5)	6 (27.3)	8 (38.1)	3 (33.3)	1(100)	1 (100)	1 (100)	-	-
Grade 3	8 (34.8)	7 (31.8)	5 (23.8)	3 (33.3)	-	-	-	-	-
Skin involvement, n (%)	22 (95.7)	21 (95.5)	19 (90.5)	5 (55.6)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
Gastrointestinal tract involvement, n (%)	1 (4.3)	4 (18.2)	5 (23.8)	1 (11.1)	-	-	-	-	-
Cardiovascular system involvement, n (%)	12 (52.2)	10 (45.5)	8 (38.1)	6 (66.7)	-	1 (100)	1 (100)	-	-
Respiratory system İnvolvement, n (%)	17 (73.9)	11 (50.0)	13 (61.9)	6 (66.7)	1 (100)	1 (100)	-	-	-
Neurological system involvement, n (%)	3 (13.0)	3 (13.6)	4 (19.0)	3 (33.3)	-	-	-	-	-
Fever, n (%)	1 (4.3)	2 (9.1)	3 (14.3)	3 (33.3)	-	-	-	-	-
Skin prick test posıtıvıty, n (%)	6 (26.1)	3 (13.6)	2 (9.5)	-	-	-	-	-	-
Intradermal test positivity, n (%)	13 (56.5)	8 (36.4)	7 (33.3)	2 (22.2)	-	-	-	-	-
Interval between skin test and HSRs (day)	39.82±28.91	193.25±538.51	47.44±61.58	35.57±22.5	31	-	-	19	5
Completion of RDD, n (%)	20 (87)	22 (100)	20 (95.2)	9 (100)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
BTRs during RDD, n (%)	13 (56.5)	2 (9.1)	7 (33.3)	-	-	-	-	-	-
Severity of BTRs during RDD(Brown), n (%)	10 (43.5)	2 (9.1)	5 (23.8)	-	-	-	-	-	-
Grade 1	1 (4.3)	-	2 (9.5)	-	-	-	-	-	-
Grade 2	2 (8.7)	-	-	-	-	-	-	-	-
Grade 3									
RDD with omalizumab, N (%)	4 (17.4)	3 (13.6)	1 (4.8)	1 (11.1)	-	1 (100)	-	-	-
RDD Scheme									
12 step	18 (78.3)	20 (90.9)	19 (90.4)	8 (88.9)	1 (100)	1 (100)	1 (100)	1 (100)	1 (100)
16 step	2 (8.7)	-	-	-	-	-	-	-	-
12 step-step down to 8	1 (4.3)	2 (9.1)	-	1 (11.1)	-	-	-	-	-
12 step-step up to 16	-	-	1 (4.8)	-	-	-	-	-	-
12 step-step up to 13	2 (8.7)	-	1 (4.8)	-	-	-	-	-	-
Cumulative chemotherapeutic agent dose until the HSR (mg)	3847.95±2211.61	501.76±395.84	1061.30±622	189.78±76.65	320	110	1554	500	600
RDD number	3.7±2.3	3.36±5	3.19±1.4	5.78±4.05	6	5	6	11	5

Mean±SD, n(%).
BTRs: breakthrough reactions, HSRs: Hypersensitivity reactions, RDD: Rapid drug desensitization.

Table 3 Comparison of demographic and clinical characteristics of patients who used omalizumab before RDD.

	Omalizumab + (n=10)	Omalizumab - (n=70)	P
Age(year)	51.60±10.11	55.87±12.35	0.300*
Gender (Female), n (%)	10 (100)	50 (71.40)	0.059**
Cigarette smoking (%)	4 (40)	35 (57.4)	0.330**
Cigarettes (packets/year)	16.75±12.99	36.62±15.45	**0.018***
Hypertension, n (%)	4 (40)	21 (30)	0.717**
Allergic Disease, n (%)			
No	7 (70)	53 (75.7)	-
Rhinitis	1 (10)	10 (14.3)	
Asthma	1 (10)	7 (10)	
Mastocytosis	1 (10)	-	
Diagnosis, n (%)			
Colorectal cancer	1 (10)	19 (27.1)	-
Over	6 (60)	19 (27.1)	
Stomach	-	4 (5.7)	
Breast	2 (20)	20 (28,6)	
Lung	-	4 (5.7)	
Endometrial	1 (10)	2 (2.9)	
Prostate	-	2 (2.9)	
Cancer Stage, n (%)			
Stage 3	2 (20)	8 (11.4)	0.605**
Stage 4	8 (80)	62 (88.6)	
Death, n (%)	4 (40)	27 (38.6)	1.000**
Atopy, n (%)	4 (40)	19 (35.8)	0.461**
Other drug HSRs, n (%)	1 (10)	5 (7.8)	1.000**

Mean±SD, n(%); *: Independent Groups T-Test; **: Fisher's Exact Test.
HSRs: Hypersensitivity reactions, RDD: Rapid drug desensitization.

Table 4 Laboratory measurements of omalizumab treated and other groups.

	Omalizumab Treated (n=10)	Other (n=70)	P
Forced expiratory volume 1 (FEV1) (%)	96.29±18.56	83.67±22.78	0.177*
Forced expiratory volume 1 (mL)	2487.14±674.57	2185.31±766.59	0.343*
Forced vital capacity(FVC) (%)	92.43±15.55	84.36±22.48	0.371*
Forced vital capacity (mL)	2854.29±649.66	2673.75±963.43	0.641*
FEV1/FVC	88.57±8.63	81.50±13.98	0.206*
White blood cells count	7784.00±4388.79	11355.45±33311.21	0.738*
Haemoglobin count	11.77±1.86	13.09±14.06	0.769*
Platelet count	222200.00±83270.37	241836.36±117251.35	0.615*
Eosinophil count	100.00±70.86	84.26±108.62	0.662*
Eosinophil (%)	1.51±1.39	150±184	0.992*
Lymphocyte count	1595.00±427.06	1314.81±910.18	0.346*
Lymphocyte (%)	24.03±10.52	23.16±15.65	0.867*
Neutrophil count	5473.00±4309.60	5280.37±4905.58	0.908*
Neutrophil (%)	65.53±14.56	67.44±17.08	0.742*
Eosinophil/Lymphocyte	0.06±0.05	0.10±0.19	0.545*
Eosinophil/Neutrophil	0.03±0.02	0.10±0.55	0.687*
IgE	232.29±286.76	96.64±137.13	0.062*
Triptase	6.65±0.91	6.01±1.68	0.630*

Mean±SD, *: Independent Groups T-Test, **: Pearson Chi-square Test, ***: Fisher's Exact Test.

Table 5 The characteristics of allergic reactions and RDD procedures in platinum and taxanes groups.

	Platinum (n=45)	Taxanes (n=32)	P
HSR developing cycles	8.09±4.31	4.03±6.42	**0.003***
Severity of HSR (Brown)			
Grade 1	14 (31.1)	13 (40.6)	0.530**
Grade 2	18 (40.0)	9 (28.1)	
Grade 3	13 (28.9)	10 (31.3)	
Skin involvement, n (%)	42 (93.3)	27 (84.4)	0.265***
Gastrointestinal tract involvement, n (%)	6 (13.3)	5 (15.6)	1.000***
Cardiovascular system involvement, n (%)	20 (44.4)	16 (50.0)	0.630**
Respiratory system involvement, n (%)	30 (66.7)	17 (53.1)	0.230**
Neurological system involvement, n (%)	7 (15.6)	6 (18.8)	0.712**
Fever, n (%)	4 (8.9)	5 (15.6)	0.477***
Skin prick test posıtıvıty, n (%)	8 (18.2)	3 (9.4)	0.339***
Intradermal test positivity, n (%)	20 (45.5)	10 (31.2)	0.211**
Interval between skin test and HSRs (day)	43.92±47.32	147.61±457.81	0.243*
Completion of RDD, n (%)	41 (91.1)	32 (100.0)	0.137***
BTRs during RDD, n (%)	20 (44.4)	2 (6.2)	**<0.001****
Severity of BTRs during RDD (Brown), n (%)			
Grade 1	15 (75.0)	2 (100.0)	-
Grade 2	3 (15.0)	0 (0.0)	
Grade 3	2 (10.0)	0 (0.0)	
Omalizumab before RDD n (%)	5 (11.1)	4 (12.5)	1.000***
RDD Scheme			
12 step	38 (84.4)	29 (90.6)	-
16 step	2 (4.4)	0 (0.0)	
12 step-step down to 8	1 (2.2)	0 (0.0)	
12 step-step up to 16	1 (2.2)	3 (9.4)	
12 step-step up to 13	3 (6.7)	0 (0.0)	
Cumulative chemotherapeutic agent dose until the HSR (mg)	2409.39±2128.93	411.13±356.01	**<0.001***
RDD number	3.49±1.93	6.34±4.68	**0.002***

Mean±SD, n(%); *: Independent Groups T-Test; **: Fisher's Exact Test.
BTRs: Breakthrough reactions, HSRs: Hypersensitivity reactions, RDD: Rapid drug desensitization.

grade 1, and 28,75 % (n = 23) were grade 3 , according to Brown's classification. The RDD has been applied to many patients with varying ınıtıal reactions.

Skin involvement was seen in 72 (80%) patients, respiratory system involvement in 49 (61.2%) patients, cardiovascular system involvement in 38 (47.5%) patients, neurological involvement in 13 (16.25%) patients, gastrointestinal system involvement in 11 (13.7%) patients, and fever in 9 (11.25%) patients.

The dose of reaction development in the platinum group was significantly higher than the taxan group (p=0.003). There was no statistical difference in the severity of reaction, system involvement, and distribution of symptoms between platinum and taxan groups (p>0.05). The rate of BTR during RDD was higher in patients receiving platinum compared with taxan (p<0.001). Similar to our study, Castel et al. also found that the platinum group had a risk factor for BTR during RDD compared to other agents.[24] BTR was observed in 22/377 (5.8%) patients during RDD. Omalizumab was administered to one patient with initial HSR grade 3. Despite this, grade 3 HSR developed during RDD. In other patients, the severity of BTR during RDD was less. Similar to our study, 141 BTRs (9.6%) developed during 1471 RDDs in the study by Caiado et al. BTRs were more common with platinum than taxanes.[24] Seventeen (21.2%) patients developed mild BTRs; 5 (6.2%) patients developed moderate to severe BTRs. In a study in which 2177 RDDs were administered to 370 patients, the incidence of moderate to severe BTRs was 7%.[25]

When HSRs developed, the cumulative chemotherapy dose was higher in patients receiving platinum than taxanes; the number of RDDs administered after the development of HSRs was lower in the platinum group (p values: p<0.001; p = 0.002). In our study, the mean total dose of platins/taxanes at HSR onset was approximately 2409 ±2128 mg/411 ±356 mg. In the literature, in a multicenter study conducted in Japan, the mean carboplatin dose for HSR was determined as 7000 mg.[26] There are no studies on dose determination in the literature for other platins and taxanes. This is the first study to give the mean dose of HSR for each agent. In general, platinum developed HSR at higher doses than taxanes.

Severe initial reactions are associated with an increased risk of BTRs during RDD.[25,27] Omalizumab is an anti-IgE

Table 6 Patients received omalizumab before RDD.

	Gender/Age	Diagnosis/ Stage	HSR responsible agent	Severity of HSR	Skin prick test/ Intradermal test	Completing RDD	BTRs during RDD	Severity of BTRs during RDD	Allergic disease	RDD	Omalizumab dose (mg)	Interval between omalizumab doses (days)	Interval between omalizumab CHT
1	F/55	Breast/4	Doksorubisin	2	-	Yes	-	-	Mastocytosis	5	300	21	2
2	F/52	Breast/4	Dasotaxel	2	Negative	Yes	-	-	-	6	300	28	2
3	F/33	Over/3	Paclitaxel	3(A)	Negative	Yes	-	-	-	10	300	28	2
4	F/49	Over/4	Paclitaxel	3(A)	Negative	Yes	-	-	-	11	300	21	2
5	F/59	Over/4	Paclitaxel	3(A)	Negative	Yes	-	-	-	1	300	21	2
6	F/56	Over/4	Karboplatin	3(A)	Negative	Yes	-	-	Asthma	3	300	28	2
7	F/49	Over/3	Karboplatin	3(A)	Negative	No	Yes	3	-	3	300	28	3
8	F/70	Endometrial/4	Karboplatin	3(A)	Positive	Yes	Yes	1	Rhinitis	3	300	28	2
9	F/53	Over/4	Karboplatin	3(A)	Positive	No	Yes	1	-	1	300	28	2
10	F/40	Colorectal cancer/4	Oksaliplatin	3(A)	Positive	Yes	Yes	2	-	2	150	28	2

A: Arrest, BTRs: Breakthrough reactions, F: Female, HSRs: Hypersensitivity reactions, RDD: Rapid drug desensitization.

monoclonal antibody. It was approved in 2003 for severe asthma and in 2014 for chronic spontaneous urticaria.[28,29] In asthma, serum total IgE level (IU/mL) and body weight (kg) determine the dose, whereas in urticaria a fixed dose is applied. However, omalizumab has also been studied as an off-label treatment for several allergic conditions. This includes its application before drug desensitization.[30] Omalizumab was administered before desensitization in 10 patients who developed anaphylaxis as an initial reaction. Eight patients developed cardiac arrest. All patients had received omalizumab 2 days before; every 21 or 28 days. The dose of omalizumab in patients was determined by making an off-label application to the Ministry of Health and obtaining approval. There was great heterogeneity in the literature between omalizumab injections and RDD. In particular, it is recommended to administer omalizumab before the first RDD and to repeat it 1 day before each RDD.[11] In four patients receiving the taxan group drugs, omalizumab was administered before RDD and BTR was not observed during RDD. Moreover, in three of these patients, the ınıtıal reaction was cardiac arrest. In the literature, omalizumab administration to a patient who developed grade 2 reaction with taxel has attracted our attention.[31] RDD could not be continued in two patients on the list. One of them discontinued RRD because grade 3 BTR developed during RDD. In the other patient, grade 1 reaction developed during RDD and the patient refused treatment.

Limitation

First, this was a retrospective study and was open to various biases. Secondly, when we looked at the patients who received omalizumab, there were also patients who developed grade 2 and 3 reactions. Because of the collection of different patient groups, a prospective study that we plan on this subject will enable us to establish clearer criteria for patient selection.

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Availability of Data and Materials

The data that support the findings of this study are not publicly available because they contain information that could compromise the privacy of research participants, but the data are available from the authors.

Ethics Approval and Consent to Participate

Approval from the Ethics Committee was obtained prior to the study at Health Sciences University, Süreyyapaşa Training and Research Hospital (116.2017.R-341). In addition, approval was obtained from the Ministry of Health to publish the data because of the off-label use of omalizumab (E-24931227-506.01-5591579).

Authors Consent for Publication

Both authors approved this manuscript for submision to the journal.

Authors Contributions

Both authors were involved in the conceptualization and methodology of the study, writing and reviewing of the original draft, and project supervision.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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