Title: Successful Desensitization with Chemotherapeutic Drugs: a Tertiary Care Center Experience

Running Head: Successful Desensitization with Chemotherapeutic Drugs

Count of Words, References and Tables: 1528 (main text), 224 (abstract), 23 (references), 3 (tables).

[1]Mehmet Erdem Çakmak, M.D.

[1]Saltuk Buğra Kaya, M.D.

[1]Özge Can Bostan, M.D.

[2]Özge Öztürk Aktaş, M.D.

[1]Ebru Damadoğlu, M.D.

[1]Gül Karakaya, M.D.

[1]Ali Fuat Kalyoncu, M.D.

[1]Hacettepe University School of Medicine Department of Chest Diseases, Division of Allergy and Clinical Immunology, Ankara, Turkey

[2]Department of Allergy and Clinical Immunology, Ankara City Hospital, Ankara, Turkey

Corresponding Author: Mehmet Erdem Çakmak

Address: Hacettepe University School of Medicine, Sıhhiye, Ankara.

E-mail: mehmeterdemcakmak@gmail.com

Phone: 0505 486 97 50

Fax number: +90 (312) 310 08 09

Keywords: chemotherapy, desensitization, drug allergy, hypersensitivity, cancer.

This study has been presented as a oral presentation at the XXVI. National Allergy and Clinical Immunology Congress between 9-13 November 2019 and presented as a poster EAACI Digital Congress 06 - 08 June 2020.

* Report no conflict of interest.

* Declare no financial disclosure.

Abstract

Introduction: Hypersensitivity reactions to chemotherapeutic drugs are increasing all over the world, and desensitization to them has become the standard treatment approach. This study aimed to evaluate the characteristics of chemotherapeutic drug hypersensitivity reactions and the outcome of desensitization procedures.

Methods: Between January 2017 and 2019, patients who have been desensitized to chemotherapeutic drugs were included retrospectively. Data were obtained from the medical records of the patients.

Results: A total of 35 patients were evaluated; of whom 24 (68.5%) were female and 11 were male (31.5%). The mean age was 54.54 ± 13.39 (min-max: 41-69) years. Colorectal cancer was the most common malignancy (n:14, 40%). Desensitization was performed with oxaliplatin in 17 (48.5%), carboplatin in nine (25.7%), paclitaxel in four (11.4%), cisplatin in two (5.7%), irinotecan in two (5.7%), rituximab in two (5.7%), and docetaxel in one (2.8%) patients. Thirty four (97.1%) were successfully desensitized without any reactions. Anaphylaxis occurred during desensitization with rituximab and the procedure could not be completed. The reactions occurred during the first administration of the chemotherapeutic agent in five (14.2%) patients. Skin tests were performed on 26 (74.2%) patients. Skin prick and intradermal tests were positive in 7 (26.9%) and 12 (46.1%) patients, respectively.

Conclusion: Desensitization is an effective and safe treatment approach for chemotherapeutic drug hypersensitivity and can be performed safely by observing general precautions to anaphylaxis.

Keywords: chemotherapy, desensitization, drug allergy, hypersensitivity, cancer.

Introduction

Various chemotherapeutic drugs are used for cancer treatment nowadays. Hypersensitivity reactions to chemotherapeutic drugs are unexpected reactions, unlike the expected toxicities of these drugs. Hypersensitivity reactions are increasing, and may occur with any chemotherapeutic drug. The severity of the reactions may vary from a mild skin rash to life-threatening anaphylactic shock (1).

The sensitivity of a tumor to certain chemotherapeutics and the necessity to choose the most effective treatment for survival, usually do not allow for selection of an alternative chemotherapeutic agents. When a hypersensitivity reaction to a chemotherapeutic drug develops, there may be no alternative medication regimens. In such cases, desensitization is the appropriate treatment approach. During desensitization, the drug is administered in small doses until the target dose is reached within a few hours. Using this procedure, temporary tolerance is achieved, and the protocol should be repeated for each treatment cycle which should be performed in experienced centers in the intensive care unit (2).

The aim of this study was to evaluate the characteristics of chemotherapeutic drug hypersensitivity reactions and the outcome of desensitization procedures.

Methods

Between January 2017 and 2019, patients who were admitted to a tertiary adult allergy outpatient clinic with hypersensitivity reactions to chemotherapeutic drugs and desensitized were included retrospectively. Data were obtained from the medical records of every patients. Patients who were younger than 18 years old and had a hypersensitivity reaction 24 hours after drug infusion were excluded from the study. In addition, desensitization was not performed to patients who developed type 2, type 3 or type 4 hypersensitivity reactions after

chemotherapeutic infusion. Initial hypersensitivity reactions of patients were classified according to the National Cancer Institute (NCI) Common Toxicity Criteria (3).

Skin prick tests and intradermal tests were performed on the volar side of the forearm with the culprit drug, with positive (histamine; 10 mg/ml) and negative (saline) controls. Skin tests were not performed on patients who had received antihistamines in the last seven days or who had dermographism, and were evaluated after 20 minutes. Skin tests were performed at least 2 weeks after the initial hypersensitivity reaction to reduce false negative results. For both the skin-prick and intradermal tests, an induration diameter of 3 mm and over was considered positive, respsectively. Drug concentrations for skin prick test and intradermal tests were performed based on other studies (4-9). Table I shows the concentration of drugs used in skin testing.

Brigham and Women's Hospital (BWH) standard 12, 16, or 20 step desensitization protocol, developed by Castells et al. (2), was performed on the patients. The most commonly used desensitization protocol was based on 12 steps. Patients with severe hypersensitivity reactions and anaphylactic reactions were desensitized with 16 steps or 20 steps (10). Premedication was initiated before infusion. Dexamethasone 20 mg orally or intravenously (iv) before 6 and 12 hours, diphenhydramine 50 mg or pheniramine 45.5 mg iv before 30 minutes, ranitidine 50 mg iv or famotidine 20 mg iv before 30 minutes, and 50 mg of oral hydroxyzine before 30 minutes were given as premedication. Chemotherapeutic drugs were administered in 250 mL of 5% dextrose or saline at 1/10000, 1/1000, 1/100, 1/10, and 1/1 dilutions.

The study protocol was approved by the Hacettepe University Faculty of Medicine Ethics Committee (no: 2020/03-33). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data were analyzed with the IBM SPSS Statistics 21 program. Descriptive statistics (mean, standard deviation, minimum and maximum value) were performed for numerical data, and frequency distributions were performed for categorical variables.

Results

A total of 35 patients were evaluated, of whom 24 (68.5%) were female and 11 were male (31.5%). The mean age was 54.54 ± 13.39 (min-max: 41-69) years. Colorectal cancer was the most common tumor in patients (n:14, 40%). Desensitization was performed with oxaliplatin in 17 (48.5%), carboplatin in nine (25.7%), paclitaxel in four (11.4%), cisplatin in two (5.7%), irinotecan in two (5.7%), rituximab in two (5.7%), and docetaxel in one (2.8%) patients. Gender distribution, the type of chemotherapeutic drugs, and malignancies are shown in Table II.

Desensitization was successful in 34 (97.1%) of 35 patients. In one patient, desensitization with rituximab could not be completed due to anaphylaxis. Allergic reactions occurred during the first chemotherapeutic cycle of treatment in five (14.2%) patients. Skin tests were performed in a total of 26 (74.2%) patients. Skin prick and intradermal tests were positive in 7 (26.9%) and 12 (%46.1) patients, respectively. Reactions, skin test results, and desensitization characteristics of the patients are shown in Table III.

Discussion

In this study, we successfully desensitized 34 of 35 (97.1%) patients who had chemotherapeutic-drug hypersensitivity. There are different desensitization protocols for various chemotherapeutic drugs in the literature. In recent years, the BWH standard desensitization protocol, developed by Castells et al. (2), has been used for all chemotherapeutic drugs. This protocol was used in the current study. A shorter protocol was developed by Madrigal-Burgaleta et al. (11) because of the long duration of the protocol developed by

Castells et al. More than 2000 desensitizations were performed with various chemotherapeutic drugs by both protocols. Desensitization was successful in 99% of patients (12).

Hypersensitivity reactions can be observed to any chemotherapeutic drugs. Reactions often occur against taxanes (paclitaxel, docitaxel), platinum-containing agents (cisplatin, carboplatin, oxaliplatin), and epipodophyllotoxins (etaposide) (13). In this study, the most common hypersensitivity reactions observed were to platinum agents and taxanes. These chemotherapeutic drugs are frequently used in more common cancers such as colon, lung, breast, stomach, and ovarian cancers. Due to the frequent use of these drugs, hypersensitivity reactions may often be observed. Hypersensitivity reactions usually occur during or after infusion. Hypersensitivity reactions to taxanes usually occur within the first few minutes of infusion during the first or second chemotherapy cycle. Taxanes rarely cause IgE-mediated hypersensitivity reactions but lead to hypersensitivity reactions generally by directly releasing mediators, such as Histamine, neutral proteases, proteoglycans, and cytokines from mast cells. Hypersensitivity reactions to platinum agents are usually observed after multiple chemotherapy cycles, which are often IgE-mediated (2,14,15). In the current study, desensitization to platinum agents and taxanes was successfully performed in 28 (80%) and five (14.2%) patients, respectively. Patients with platinum allergy had hypersensitivity reactions after multiple cycles of platinum-containing chemotherapy, usually for treatment of colon and ovarian cancer.

In a single patient in our study, desensitization with rituximab could not be completed due to anaphylaxis. A hypersensitivity reaction developed in the second chemotherapy cycle with rituximab in this patient. When this desensitization process was unsuccessful, we increased the number of the desensitization step. The 16-step desensitization procedure also proved unsuccessful. Thereafter, we planned a 20-step desensitization procedure, but the patient refused, due to the previous severe allergic reaction, and a different chemotherapy regimen was planned by the oncologist. Hypersensitivity to rituximab is often observed after the first

chemotherapy cycle. Urticaria, hypotension, anaphylaxis, angioedema, bronchospasm, acute lung injury, cardiogenic shock, and, in some cases, death have been reported within two hours of infusion of rituximab (16). Desensitization with rituximab is usually successful according to literature (17,18).

Desensitization with irinotecan was successful in two patients with colon cancer in the current study. Irinotecan is a chemotherapeutic agent commonly used in the treatment of gastrointestinal malignancies. Hypersensitivity reactions with irinotecan are less common than with other chemotherapeutics. Successful desensitization with irinotecan has been reported in a few case reports in the literature (19,20).

Although clinical history is important in the diagnosis of drug allergies, the diagnosis can be supported by skin tests. Allergic reactions to platinum agents are usually type I immunological reactions. Reactions to taxanes are usually mediated by mast cell degranulation or complement activation. Skin tests provide reliable results for platinum allergies. However, the role of skin tests in the diagnosis of taxane allergy is limited (13-15). In a multi-center study investigating the role of skin tests in the diagnosis of immediate hypersensitivity reactions to taxanes, prick test results were negative in all patients. Intradermal test results were positive in 14 patients (10 paclitaxel [15.9%] and 4 docetaxel [19%]). The authors stated that the skin test is useful in the diagnosis of taxan allergies (21). Positive skin tests were frequently observed to oxaliplatin in the current study. Positive intradermal tests were observed in eight (57.1%) of 14 patients with oxaliplatin and in one (20%) of 5 patients with taxanes. Skin tests for oxaliplatin allergy are highly sensitive. The sensitivity of the skin test was between 75% and 100% in several studies (6, 22, 23). In this study, we observed lower skin-test positivity with platinum agents compared to previous data in the literature. We could not perform skin tests on all of the patients for various reasons: dermographism, recent use of antihistamines, etc. In addition, these patients receive chemotherapy at frequent intervals; therefore, when they are admitted to our allergy

clinic, it may not be the appropriate time to perform skin tests. Skin-test positivity may have been low due to this reason.

In conclusion, desensitization is an effective and safe treatment approach for chemotherapeutic drug hypersensitivity and can be performed safely by following general precautions to anaphylaxis.

Acknowledgements

We sincerely thank to Ebenezer M. Awuah-Yeboah for language editing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

1. Lee C, Gianos M, Klaustermeyer WB. Diagnosis and management of hypersensitivity reactions related to common cancer chemotherapy agents. Ann Allergy Asthma Immunol 2009;102:179-87.
2. Castells M. Drug desensitization in oncology: Chemotherapy agents and monoclonal antibodies. In: Pichler WJ (ed). Drug Hypersensitivity. Basel, Karger, 2007:413-25.
3. National Cancer Institute: Common Terminology Criteria for Adverse Events. Version 5.0.Index. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Published: November 27, 2017.
4. Lee CW, Matulonis UA, Castells MC. Carboplatin hypersensitivity: a 6-h 12-step protocol effective in 35 desensitizations in patients with gynecological malignancies and mast cell/IgE-mediated reactions. Gynecol Oncol 2004;95:370-6.
5. Lee CW, Matulonis UA, Castells MC. Rapid inpatient/outpatient desensitization for chemotherapy hypersensitivity: standard protocol effective in 57 patients for 255 courses. Gynecol Oncol 2005;99:393-9.
6. Garufi C, Cristaudo A, Vanni B, Bria E, Aschelter AM, et al. Skin testing and hypersensitivity reactions to oxaliplatin. Ann Oncol 2003;14:497-8.
7. Picard M, Purl, Caiado J, Giavina-Bianchi P, Galvão VR, et al. Risk stratification and skin testing to guide re-exposure in taxane-induced hypersensitivity reactions. J Allergy Clin Immunol 2016; 137:1154.
8. Wong JT, Long A. Rituximab hypersensitivity: evaluation, desensitization, and potential mechanisms. J Allergy Clin Immunol Pract 2017;5(6):1564-71.
9. Alvarez-Cuesta E, Madrigal-Burgaleta R, Angel-Pereira D, Ureña-Tavera A, Zamora-Verduga M, et al. Delving into cornerstones of hypersensitivity to antineoplastic and

biological agents: value of diagnostic tools prior to desensitization. Allergy. 2015;70(7):784-94.

10. Castells Guitart MC. Rapid drug desensitization for hypersensitivity reactions to chemotherapy and monoclonal antibodies in the 21st century. J Investig Allergol Clin Immunol 2014;24(2):72-9.
11. Madrigal-Burgaleta R, Beges-Gimeno MP, Angel-Pereira D, Ferreiro Monteagudo R, Guillen-Ponce C, et al. Hypersensitivity and desensitization to antineoplastic agents: outcomes of 189 procedures with a new short protocol and novel diagnostic tools assesssment. Allergy 2013;68:853-61.
12. Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, et al. Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. J Allergy Clin Immunol 2008;122:574-80.
13. Gomes ER, Demoly P. Epidemiology of hypersensitivity drug reactions. Curr Opin Allergy Clin Immunol 2005;5:309-16.
14. Ruggiero A, Triarico S, Trombatore G, Battista A, Dell'Acqua F, et al. Incidence, clinical features and management of hypersensitivity reactions to chemotherapeutic drugs in children with cancer. Eur J Clin Pharm 2013;69:1739-46.
15. Lenz HJ. Management and Preparedness for Infusion and Hypersensitivity Reactions. Oncologist 2007;12:601-9.
16. Hong DI, Bankova L, Cahill KN, Kyin T, Castells MC, et al. Allergy to monoclonal antibodies: cutting-edge desensitization methods for cutting-edge therapies. Expert Rev Clin Immunol 2012;8:43-54.
17. Wong JT, Long A. Rituximab hypersensitivity: evaluation, desensitization, and potential mechanisms. J Allergy Clin Immunol Pract 2017;5(6): 1564-71.

18. Cansever M, Ozcan A, Dursun I, Unal E, Tahan F. Successful Rapid Desensitization of Two Teenagers with Rituximab Hypersensitivity. J Clin Diagn Res 2019;13(5): 01-03.
19. Cubero JL, Escudero P, Yubero A, Millán P, Sagredo MA, et al. Successful Desensitization to Irinotecan After Severe Hypersensitivity Reaction. J Investig Allergol Clin Immunol 2016;26(5):314-316.
20. Abu-Amna M, Hassoun G, Hadad S, Haim N, Bar-Sela G. Successful Desensitization Protocol for Hypersensitivity Reaction Caused by Irinotecan in a Patient With Metastatic Colorectal Cancer. Clin Colorectal Cancer 2015;14(4):e49-51
21. Pagani M, Bavbek S, Dursun AB, Bonadonna P, Caralli M, et al. Role of Skin Tests in the Diagnosis of Immediate Hypersensitivity Reactions to Taxanes: Results of a Multicenter Study. J Allergy Clin Immunol Pract 2019;7(3):990-997.
22. Pagani M, Bonadonna P, Senna GE, Antico A. Standardization of skin test for diagnosis and prevention of hypersensitivity reactions to oxaliplatin. Int Arch Allergy Immunol 2008;145:54-57.
23. Meyer L, Zuberbier T, Worm M, Oettle H, Riess H. Hypersensitivity reactions to oxaliplatin: crossreactivity to carboplatin and the introduction of a desensitization schedule. J Clin Oncol 2002;20:1146-47.

Table I. The concentrations of drugs used in skin testing.

Drug	**Prick test (mg/mL)**	**İntradermal test (mg/mL)**
Carboplatin	10	1, 10
Cisplatin	1	0.1, 1
Oxaliplatin	5	0.5, 5
Paclitaxel	1	0.001, 0.01
Docetaxel	0.4	0.004, 0.04
Rituximab	10	0.1, 1, 3
İrinotecan	20	2

Table II. Gender, malignancies and chemotherapeutic drugs

Malignancy	**Gender (m/f)#**	**Oxaliplatin**	**Carboplatin**	**Cisplatin**	**Paclitaxel**	**Docetaxel**	**İrinotecan**	**Rituximab**
Colorectal	6/8	12					2	
Ovarian	-/6		6		1			
Gastric	3/1	3				1		
Endometrial	-/3		1	1	2			
Lymphoma	-/2							2
Malignant melanoma	-/1				1			
Breast	-/1	1						
Larynx	1/-			1				
Lung	1/-		1					
Peritoneal	-/1		1					
Cholangio-cellular	-/1	1						
Total	11/24	17(%48.5)	9 (%25.7)	2 (%5.7)	4 (%11.4)	1 (%2.8)	2 (%5.7)	2 (%5.7)

m: male, f: female

Table III. Desensitization results, skin tests and systemic symptoms of chemotherapeutic drugs before desensitization

No	Malignancy	Drug	Reaction	Reaction developing cycle	Skin Tests		Desensitization steps
					Prick	İntradermal	
1	Gastric	Docetaxel	Flushing, dyspnea	3	Negative	Pozitive	12
2	Malignant melanoma	Paclitaxel	Urticaria, dyspnea	1	Negative	Negative	12
3	Endometrial	Paclitaxel	Urticaria, dyspnea	1	Negative	Negative	12
4	Ovarian	Paclitaxel Carboplatin	Urticaria, dyspnea	14	Negative	Negative	12
5	Endometrial	Paclitaxel Carboplatin	Flushing, angioedema	7	Negative	Negative	12
6	Ovarian	Carboplatin	Urticaria, dyspnea	9	Not performed		12
7	Ovarian	Carboplatin	Urticaria, dyspnea	8	Negative	Negative	12
8	Lung	Carboplatin	Flushing, dyspnea	4	Negative	Negative	12
9	Ovarian	Carboplatin	Urticaria, dyspnea	15	Negative	Negative	12
10	Ovarian	Carboplatin	Nausea, vomiting, dyspnea	14	Not performed		12
11	Peritoneal	Carboplatin	Urticaria, dyspnea	6	Positive	Positive	20
12	Ovarian	Carboplatin	Urticaria, dyspnea, hypotension	8	Not performed		20
13	Gastric	Oxaliplatin	Nausea, vomiting, tachycardia	2	Negative	Positive	12
14	Colorectal	Oxaliplatin	Flushing, dyspnea, angioedema	13	Pozitive	Positive	12
15	Colorectal	Oxaliplatin	Urticaria, dyspnea	3	Negative	Negative	12
16	Colorectal	Oxaliplatin	Flushing, dyspnea	4	Not performed		12
17	Colorectal	Oxaliplatin	Flushing, hypotension	2	Negative	Negative	12
18	Cholangio-cellular	Oxaliplatin	Urticaria, tachycardia	3	Negative	Negative	12
19	Gastric	Oxaliplatin	Urticaria, dyspnea, hypotension	6	Negative	Negative	12
20	Colorectal	Oxaliplatin	Urticaria, dyspnea	10	Positive	Positive	12
21	Colorectal	Oxaliplatin	Urticaria, dyspnea	9	Negative	Positive	12
22	Gastric	Oxaliplatin	Angioedema, dyspnea	5	Negative	Negative	12
23	Colorectal	Oxaliplatin	Urticaria, abdominal pain	14	Pozitive	Positive	12
24	Colorectal	Oxaliplatin	Urticaria, dyspnea	10	Not performed		16
25	Colorectal	Oxaliplatin	Urticaria, dyspnea	16	Positive	Positive	16
26	Colorectal	Oxaliplatin	Flushing, dyspnea	8	Not performed		16
27	Colorectal	Oxaliplatin	Flushing, dyspnea	9	Negative	Positive	20
28	Colorectal	Oxaliplatin	Flushing, angioedema	5	Pozitive	Positive	20
29	Breast	Oxaliplatin	Dyspnea, hypotension	1	Negative	Negative	20
30	Larynx	Cisplatin	Dyspnea	2	Not performed		12
31	Endometrial	Cisplatin	Urticaria, dyspnea	6	Negative	Positive	16
32	Colorectal	Irinotecan	Nausea, vomiting	1	Not performed		12
33	Colorectal	Irinotecan	Nausea, vomiting, hypotension	2	Pozitive	Positive	16
34	Lymphoma	Rituximab*	Urticaria, flushing, dyspnea, angioedema	2	Negative	Negative	16
35	Lymphoma	Rituximab	Chest pain, dyspnea	1	Not performed		16

*Desensitization was not succesful