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Oxaliplatin-induced hypersensitivity reactions: risk factors and management

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Abstract. – OBJECTIVE: Chemotherapy-related adverse reactions have been steadily increasing in recent years. In patients who develop oxaliplatin-induced hypersensitivity reactions (HSRs), prognosis and quality of life are adversely affected. Proper management of cancer patients enables them to safely receive first-line treatments. This study aimed to assess the risk factors in oxaliplatin-induced HSRs and the effectiveness of the rapid desensitization protocol.

PATIENTS AND METHODS: In the study, 57 patients treated with oxaliplatin between October 2019 and August 2020 in the Medical Oncology Department of Elazig City Hospital were retrospectively evaluated. We analyzed patients' clinical histories to reveal any associations with the development of oxaliplatin-induced HSRs. Moreover, we re-evaluated 11 patients with oxaliplatin-induced HSRs through infusion time or desensitization procedures.

RESULTS: Of 57 patients treated with oxaliplatin, 11 (19.3%) had HSRs. Patients with HSRs were younger and had higher peripheral blood eosinophil counts than those without HSRs (p=0.004, p=0.020, respectively). Prolongation of the infusion time was effective in the re-administration of oxaliplatin in six of the hypersensitive patients. Rapid desensitization protocol was performed for a total of 11 cycles in four patients with recurrent HSRs, and their chemotherapy regimens were successfully completed.

CONCLUSIONS: This retrospective study has revealed that younger ages and higher peripheral eosinophil counts could be predictive for oxaliplatin-induced HSR. Furthermore, the study confirms that prolongation of the infusion time and rapid desensitization protocol are effective in patients with HSRs.

Key Words:
Oxaliplatin, Hypersensitivity reaction, Desensitization, Chemotherapy.

Introduction

Chemotherapy drugs are widely used to treat malignant tumors. Oxaliplatin is a third-generation platinum group anti-neoplastic agent and is a standard treatment option for some gastrointestinal malignancies. Oxaliplatin is typically administered in combination with fluorouracil and leucovorin (FOLFOX regimen) or capecitabine (XELOX regimen)[1,2]. Oxaliplatin-related adverse events such as neurotoxicity, hematologic toxicity, gastrointestinal toxicity, and hypersensitivity reactions (HSRs) may occur during treatment[1,3]. HSRs usually occur within the first hour of infusion, and clinical manifestations range between mild and severe reactions. The most common symptoms in patients experiencing hypersensitivity are flushing, pruritus, urticaria, angioedema, and skin manifestations that may progress to generalized erythema. Dizziness, diarrhea, bronchospasm, tachycardia, and blood pressure changes might occur as well. In severe cases, hypotension, cardiovascular collapse, and even death occur[3-5].

In recent years, with the increase in the use of oxaliplatin-based chemotherapy, the incidence of oxaliplatin-related HSRs has increased to 8.9-24%[1,2]. Immunoglobulin (Ig)-E-mediated type I hypersensitivity has been shown[4] to be the main mechanism of immediate type HSRs developing against oxaliplatin. Skin tests have been used to predict hypersensitivity in these IgE-mediated reactions. These tests have a negative predictive value of 56%-95% and a positive predictive value of 92%-100% in oxaliplatin hypersensitive patients, depending on the population[4]. Oxaliplatin-induced HSRs may interrupt the process of chemotherapy for some cancer patients. This situation delays disease control and may shorten overall survival[1]. Rapid drug desensitization (RDD) protocols provide a temporary tolerance to chemotherapeutics in patients who develop immediate-type HSRs and enable the safe administration of necessary chemotherapeutics. Besides, it also protects against severe HSRs and prevents further delays in treatment in critically ill patients by allowing patients to receive the desired medication within minutes to hours[4,6].

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This retrospective study aimed to investigate the clinical characteristics and risk factors of oxaliplatin-induced HSRs. We also sought to analyze the effectiveness of the desensitization protocol we applied.

Patients and Methods

Patients

In this study, we retrospectively analyzed the medical records of 57 patients who received an oxaliplatin-based chemotherapy regimen in the Medical Oncology department of Elazig City Hospital between October 1, 2019, and August 1, 2020. All patients received premedication with dexamethasone 16 mg intravenously (iv), ranitidine 50 mg iv, and pheniramine maleate 45.5 mg iv 30 minutes before the oxaliplatin infusion. Each oxaliplatin treatment (85 mg/m^2 or 130 mg/m^2) takes two hours. Immediate-type HSRs were considered mild (grade I), moderate (grade II), or severe (grade III) based on Brown's classification[7]. In 11 patients who developed oxaliplatin-induced HSRs, the infusion time of oxaliplatin was prolonged (6-8 hours) in subsequent cycles.

The standard 12-step desensitization protocol developed by Castells et al[8] was used in four patients with recurrent HSRs. For all four patients, the medical oncologist was consulted, who suggested that oxaliplatin-based chemotherapy was the most effective treatment to treat the underlying diseases.

Skin Test Protocol

Skin tests with oxaliplatin were performed at least two to four weeks after the initial reaction in patients who developed recurrent HSRs. Skin prick tests and intradermal tests were performed on the volar side of the forearm with oxaliplatin. A positive reaction was considered a wheal with a diameter 3 mm larger than that produced by a negative control (0.9% saline). Histamine (10 mg/mL) was used as a positive control. For skin prick testing, undiluted (1:1) oxaliplatin 5 mg/mL was applied and read after 15-20 min. If negative, 1:100 and 1:10 dilutions were used for intradermal tests, respectively.

Desensitization Protocol

We applied the 12-step desensitization protocol described by Castells et al[8] which is evaluated to be the best in the literature. The 12-step protocol with oxaliplatin was prepared as three solutions in 250 mL of 5% dextrose at dilutions of 1:100, 1:10, and 1:1. Each solution was administered in four steps at increasing infusion rates. The final step consists in applying the remaining concentration at a constant rate to reach the target dose. We used a volumetric infusion pump to ensure accurate infusion rates and volumes. We administered 11 RDDs in four patients who experienced immediate-type HSRs. Premedication was given 30 minutes before all desensitization procedures. Methylprednisolone 40 mg iv, pheniramine maleate 45.5 mg iv, and ranitidine 50 mg iv were given as premedication.

Statistical Analysis

Descriptive statistics were presented as frequencies, percentages, means, and standard deviations (SD). The Chi-squared test and Fisher's exact test were used to compare categorical variables. Since the sample size of one of the compared groups was smaller than 30 (11 patients with an HSR), the Mann-Whitney U test was used to compare numerical variables between groups. The independent risk factors for HSRs were examined using logistic regression analysis by including age (years), eosinophil counts in peripheral blood, and the total number of cycles as independent variables. The level of statistical significance was set at $p<0.05$. All analyses were performed using the SPSS 25.0 (IBM Corp., Armonk, NY, USA) software package.

Results

A total of 57 patients aged between 27 and 78 years treated with oxaliplatin were included in the study. About 91.2% had colorectal cancer, and 8.8% had stomach or pancreas cancer. Patient characteristics are summarized in Table I. HSRs were observed in 11 of the 57 patients (19.3%).

Patients participating in the study received one to seven cycles of oxaliplatin. The median number of cycles did not differ significantly between the groups with and without a hypersensitivity reaction (Mann-Whitney U Z=-0.923, p=0.356, Table II). The frequency of HSRs did not differ by sex, platin usage history, or atopy history. Patients with HSRs were younger than patients without HSRs. Eosinophil counts in peripheral blood were higher in patients with HSRs than in patients without HSRs. There was no significant difference between the HSR groups regarding the median body surface area (BSA, m^2), total oxaliplatin (mg), or the total number of cycles (Table II).

The variables of age, eosinophil counts in peripheral blood, and the total number of cycles were entered into a logistic regression model to

Table I. Descriptive findings.

Patient characteristics (n = 57)		Mean (Range)	n (%)
Age (years)		60.60 (27-78)	
Sex, male			29 (50.9)
Atopic diseases, yes			11 (19.3)
Diagnosis	Colorectal		52 (91.2)
	Stomach		2 (3.5)
	Pancreas		3 (5.3)
Disease stage	I		19 (33.3)
	II		4 (7.0)
	III		16 (28.1)
	IV		18 (31.6)
Chemotherapy regimen	FOLFOX		27 (47.4)
	XELOX		30 (52.6)
Platin usage history, yes		11 (19.3)	
BSA (m^2)		1.74 (1.49-2.23)	
Eosinophil count in peripheral blood (mm^3)		91.40 (10-350)	
Cumulative oxaliplatin dose (mg)		728.95 (130-1,750)	
Total chemotherapy cycles		4.07 (1-7)	
Patients with a hypersensitivity reaction			11 (19.3)
BSA: Body surface area			

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predict HSRs. The overall model was significant (Chi-square=12.104, p=0.007, Nagelkerke R^2=0.309). This model could predict HSRs with a sensitivity of 36.4% and a specificity of 93.5%. In the logistic regression analysis, age had a negative effect on the probability of having HSRs with an odds ratio of 0.923. The estimated odds ratio indicates an increase in HSRs of approximately 8% for each unit decrease in age. On the other hand, the predictor variables of eosinophil count in peripheral blood and the total number of cycles were not significant (Table III).

Table II. Distributions of the studied variables between the hypersensitivity reaction groups.

		Patients with HSR (n=11)	Patients without HSR (n=46)	Test statistics	*p*-value
		n (%)/Median (IQR)	n (%)/Median (IQR)		
Median age (years)		53 (47.00-58.00)	65 (57.75-69.00)	**-2.844**#	**0.004**
Sex	Female (n=28)	7 (25.0)	21 (75.0)	1.149*	0.284
	Male (n=29)	4 (13.8)	25 (86.2)		
Platin usage history	Yes (n=11)	2 (18.2)	9 (81.8)	0.011**	1.000
	No (n=46)	9 (19.6)	37 (80.4)		
Atopic diseases	Yes (n=11)	4 (36.4)	7 (63.6)	2.449**	0.195
	No (n=46)	7 (15.2)	39 (84.8)		
BSA (m^2)		1.70 (1.60-1.80)	1.75 (1.61-1.85)	-0.549#	0.583
Eosinophil count in peripheral blood (mm^3)		110 (80.00-200.00)	50 (30.00-120.00)	**-2.334**#	**0.020**
Cumulative oxaliplatin dose (mg)		840 (420.00-1,020.00)	735 (442.50-920.00)	-0.607#	0.544
Total number of cycles		5 (3.00-6.00)	4 (2.75-6.00)	-0.923#	0.356

BSA: Body surface area, *Chi-Square test (two sided), **Fisher's exact test (two sided), #Mann-Whitney U test Z value.

Table III. Logistic regression analysis computer output.

	B	S.E.	Wald	*p*-value	Exp (B)	95% CI for EXP (B)	
						Lower	Upper
Age (years)	-0.080	0.036	4.867	**0.027**	0.923	0.860	0.991
Eosinophil count in peripheral blood (mm^3)	0.008	0.005	2.295	0.130	1.008	0.998	1.018
Total number of cycles	0.201	0.235	0.733	0.392	1.223	0.771	1.939
Constant	1.500	2.132	0.495	0.482	4.483		

Dependent variable: Hypersensitivity reaction (no=0, yes=1), CI: Confidence interval.

Discussion

In recent years, survival has improved thanks to increased chemotherapy options for cancer patients, but the risk of allergies has also increased due to longer exposure to these treatments[1,9]. In general, the incidence of oxaliplatin-induced HSRs is reported to be 8.9%-24%[1]. In our study, we detected HSRs in 19.3% of patients. Although there are studies[1] investigating the risk factors of oxaliplatin-induced HSRs in the literature, a consensus has yet to be reached. In our study, no significant difference was found in terms of the sex of patients who developed HSRs, but being younger was found to be a risk factor (p=0.284, p=0.004, respectively). In the study by Song et al[10] descriptive and multivariate logistic regression analyses revealed that there was no significant difference between patients with and without HSRs in terms of age or sex. A meta-analysis[1] investigating potential risk factors for oxaliplatin-induced HSRs demonstrated that age was not a risk factor. However, except for one study in this meta-analysis, younger patients appear to be more likely to develop HSRs. In the same meta-analysis report[1], as in our study, no relationship was found between HSRs and sex. Okayama et al[11] stated that the risk of oxaliplatin-induced HSRs was higher in males. However, some researchers suggest[12,13] that oxaliplatin-induced HSRs are more likely to develop in females. Further research is needed to elucidate whether age and sex have a significant impact on oxaliplatin-induced HSRs.

Another significant result of our study was that the eosinophil counts in peripheral blood were higher in patients with HSRs (p=0.02). In a retrospective study by Okayama et al[11] it was reported that a higher number of peripheral eosinophils could be a predictor for oxaliplatin-induced HSRs. Eosinophils are considered to mediate HSRs, so some mechanisms may exist for the development of oxaliplatin-induced HSRs in patients with high eosinophil counts.

Steroid and antihistamine (H1 and H2) premedication may prevent mild/moderate reactions, but not severe IgE-mediated reactions[14]. Ohta et al[15] reported that dexamethasone premedication was not associated with oxaliplatin hypersensitivity. Yamauchi et al[16] suggested that dexamethasone doses lower than 12 mg were a risk factor for oxaliplatin hypersensitivity reactions. All patients in our study received dexamethasone 16 mg, H1, and H2 antihistamine before oxaliplatin treatment. The dosage of dexamethasone and other drugs used in premedication might affect oxaliplatin-induced HSRs. Yet, there are currently no guidelines or standard recommendations in this regard.

In six of 11 patients who developed oxaliplatin-induced HSRs, no recurrent HSR was observed after prolonged oxaliplatin infusion in subsequent cycles. However, recurrent HSRs were observed in five patients. One patient (grade-3 HSR) who developed recurrent HSRs refused the recommended RDD. The other four patients underwent a total of 11 RDD protocols, and all successfully completed the oxaliplatin infusion. Prolonging the oxaliplatin infusion time is an effective measure for the management of HSRs[17,18]. Consistent with our results, prolonging the infusion time may be considered in younger patients and those with higher eosinophil counts.

RDD is the only available technique for patients to safely receive a first-line drug to which they are allergic. RDD is generally considered when no alternative drug is available, however, it is widely accepted that RDD should also be considered when the allergic drug is more effective[19]. The 12-step RDD protocol followed in our study is one of the well-known protocols applied in the desensitization of chemotherapeutics[8,19]. In the study examining this protocol described by Castells et al[8] 413 desensitizations (212 to carboplatin, 12 to cisplatin, and one to oxaliplatin) were performed in 98 patients. During the desensitization proce-

dure, 67% of the patients had no reaction, whereas 27% had cutaneous reactions requiring only antihistamine. Meanwhile, severe reactions in 6% of the patients could be controlled with antihistamines, steroids, and intermediate infusion steps. After that the reactions that occurred during the desensitization procedure were resolved, the procedure could be continued, and all patients were able to receive the targeted full dose[8]. Desensitization reactions observed in a total of three cycles in our two patients were mild and treated with H1 antihistamine and methylprednisolone. In another study[20] applying the same RDD protocol, desensitization was performed a total of nine times in two patients who developed HSRs with oxaliplatin, and was completed without any reaction.

Limitations

The main limitations of our study are that it was retrospective and was conducted with a small group of patients. Nevertheless, the majority of studies investigating oxaliplatin-induced HSRs in the literature are retrospective. Another limitation of our study is that oxaliplatin-specific IgE levels were not quantified. Especially in patients in whom skin tests cannot be performed, measuring these levels may also be useful for the diagnosis of HSRs.

Conclusions

This retrospective study was conducted to assess the risk factors for oxaliplatin-induced HSRs and the effectiveness of the desensitization protocol. Our findings suggest that young age and high peripheral eosinophil counts might increase the risk of HSRs. Moreover, although our results suggest that desensitization procedures may be an effective treatment option for oxaliplatin-induced HSRs, a standard protocol optimized for the effectiveness and tolerability of treatment procedures needs to be established for more consistent results.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

The study was accomplished according to the guidelines of the Helsinki Declaration and verified by the Clinical Research Ethics Committee of Fırat University, Elazıg, Turkey (approval number: 17.09.2020/12-11).

Informed Consent

Written informed consent was obtained from all participations.

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Authors' Contributions

All the authors have made substantial contributions to the conception and design of the study, data acquisition, or data analysis and interpretation, drafting of the article or critically revising it for important intellectual content, final approval of the version to be submitted.

Availability of Data and Materials

The data that support the findings of this study are available on request from the corresponding author.

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