ORIGINAL ARTICLE

A New Practical Desensitization Protocol for Oxaliplatin-Induced Immediate Hypersensitivity Reactions: A Necessary and Useful Approach

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Abstract

Background and Objective: Desensitization protocols for patients with immediate hypersensitivity reactions (IHSRs) have proven to be effective, but they are not widely used in clinical practice because of impracticalities such as high cost, long procedure duration, and a lack of trained personnel. We aimed to determine the clinical characteristics of oxaliplatin-induced IHSRs and assess measures to protect against these reactions and to validate a new practical desensitization protocol.
Methods: We retrospectively reviewed 2640 cases of oxaliplatin IHSRs in 271 oxaliplatin users and prospectively used a newly designed desensitization protocol 32 times in 12 patients with hypersensitivity to platinum-based chemotherapy. The protocol consisted of increases in infusion rate every 15 minutes, regardless of the concentration of the chemotherapy agent in the infusion bags.
Results: Of the 271 patients administered oxaliplatin, 45 (16.6%) experienced IHSRs. Of 39 patients who experienced an IHSR but needed to continue oxaliplatin, 6 (15.4%) stopped treatment due to the reaction, and 33 (84.6%) continued despite the risk of further reactions. The new desensitization protocol was successfully completed in 12 patients (100%), but it was ineffective in 3 patients (all with a negative skin prick test), who experienced fever without urticaria.
Conclusions: Many patients who experience oxaliplatin-induced IHSRs are required to stop first-line oxaliplatin-based chemotherapy or to continue without desensitization, with the associated risks. Our new desensitization protocol is practical and easy to use in clinical practice.

Key words: Chemotherapy. Cisplatin. Desensitization. Hypersensitivity. Oxaliplatin. Platinum. Skin test.

Resumen

Introducción y Objetivos: El protocolo de desensibilización en los pacientes con reacciones de hipersensibilidad inmediata a quimioterápicos resulta efectivo, sin embargo no se aplica en muchos hospitales debido a su alto coste, consumo de tiempo y falta de personal entrenado. El motivo de este trabajo fue analizar las características clínicas y las medidas habitualmente adoptadas en esta patología y validar un nuevo protocolo de desensibilización a oxaliplatino.
Métodos: Para ello revisamos retrospectivamente 2.640 reacciones de hipersensibilidad inmediata a oxaliplatino en 271 pacientes sometidos a tratamiento con este quimioterápico. De forma prospectiva, aplicamos un nuevo protocolo de desensibilización 32 veces en 12 pacientes con hipersensibilidad inmediata a quimioterapia basada en oxaliplatino. Este nuevo protocolo se realizó con la administración escalonada de la concentración determinada cada 15 minutos.
Resultados: En cuanto a los resultados obtenidos, de los 271 pacientes a los que se administró oxaliplatino, 45 (16,6%) presentaron reacciones de hipersensibilidad inmediata. De los 39 que necesitaron seguir el tratamiento con oxaliplatino, 6 (15,4%) abandonaron el tratamiento y 33 (84,6%) continuaron. El nuevo protocolo de desensibilización se completó en 12 pacientes (100%) si bien tres de ellos manifestaron fiebre sin urticaria y una respuesta negativa en la prueba cutánea.

Conclusiones: En conclusión, una proporción importante de pacientes que sufren reacciones de hipersensibilidad a oxaliplatino interrumpen el tratamiento o lo mantienen sin ser sometidos a protocolos de desensibilización. El protocolo de desensibilización que proponemos en este estudio es fácil y muestra resultados satisfactorios en la práctica clínica.

Palabras clave: Quimioterapia. Cisplatino. Desensibilización. Hipersensibilidad. Oxaliplatino. Platino. Prueba cutánea.

Introduction

Oxaliplatin, a platinum-containing agent, is a first-line drug treatment for colorectal cancer [1]. However, between 12% and 24% of patients have been reported to experience immediate hypersensitivity reactions (IHSRs) to this drug [2-4], and the prevalence of reactions is rising at a rate parallel to that of oxaliplatin use [5-7]. As oxaliplatin IHSRs usually occur on re-exposure, numerous patients discontinue oxaliplatin-based chemotherapy. Replacement of oxaliplatin with another agent, however, can negatively affect survival. In clinical practice, many clinicians continue to use oxaliplatin-containing regimens in patients who have experienced reactions. Rather than attempting desensitization, however, they use a premedication strategy consisting of corticosteroids and/or antihistamines. The patient remains at risk of an IHSR, which can cause urticaria, angioedema, anaphylaxis, and even death.

Although many studies have evaluated the predictive factors for oxaliplatin-induced IHSRs, the findings remain controversial. To date, number of oxaliplatin administrations is the only unanimously accepted predictor. It has been widely suggested that IHSRs to oxaliplatin occur during the seventh, eighth, or ninth infusion [6,8-12], but there have been some reports of IHSRs occurring during the third infusion [10,13]. To ensure safe administration of oxaliplatin-containing regimens, leading institutes have attempted desensitization protocols [10,14-17], with almost all studies showing high success rates. The most widely used desensitization protocol is the classic 12-step protocol described by Castells et al [17], in which the infusion rate is doubled every 15 minutes, from 2 mL/min to 80 mL/min. In this protocol, infusion rates vary according to the infusion bags, which contain various concentrations of oxaliplatin. Although this protocol is known to be highly successful, it has many limitations in actual practice. Many hospitals have yet to use the protocol because of its high cost, long duration, and lack of trained health professionals. More suitable desensitization protocols are needed for real practice and as a result, some hospitals have designed new protocols [18]. At our hospital, we developed a new protocol that is easy and convenient for use in routine practice. It is an 11-step protocol in which the infusion rate is regularly increased from 60 mL/min to 120 mL/min or 240 mL/min, regardless of the concentration of oxaliplatin in the infusion bags. We believe that this modified protocol is more convenient and will help to reduce errors in clinical practice.

We were interested in understanding the clinical characteristics and predictors of oxaliplatin IHSRs and of analyzing the effectiveness of our new desensitization protocol. To this end, we retrospectively reviewed 2640 cases of oxaliplatin-based chemotherapy in 218 patients to determine the clinical characteristics of oxaliplatin-induced IHSRs in clinical practice and assess measures used to protect against these reactions. We then prospectively used the newly designed desensitization protocol in 32 cases of platinum-based chemotherapy IHSR in 12 patients to test its validity.

Methods

Patients

We enrolled 271 patients who were scheduled to receive an oxaliplatin-containing chemotherapy regimen upon admission to the Severance Hospital in Korea between March 1, 2013 and March 31, 2013. We retrospectively reviewed the patients' medical records and analyzed 2640 cases of oxaliplatin-induced IHSRs in these 271 patients. All the patients had been pretreated with 8 mg of dexamethasone and 4 mg of chlorpheniramine maleate administered intravenously 30 minutes before oxaliplatin infusion.

The desensitization protocol was used in 12 patients between May 1, 2014 and May 31, 2015. All 12 patients had experienced IHSRs to platinum-based chemotherapy (oxaliplatin or cisplatin), and based on the oncologist's opinion, they required additional platinum-based chemotherapy to treat their underlying disease. In cases where the patient had received a platinum-based chemotherapy regimen differing in dosage from the original regimen, we counted the number of cycles from the first platinum-based regimen.

Skin Test Protocol

The 12 patients who received platinum-based chemotherapy using the newly designed desensitization protocol underwent a skin test 30 minutes before the start of the protocol. We intradermally injected the platinum-based chemotherapy agent into the middle portion of the patient's forearm. The concentrations and amounts of oxaliplatin and cisplatin were 5 mg/mL and 0.03 mL and 1 mg/mL and 0.03 mL, respectively. Results were read 15 minutes after injection. Positive reactions were defined as a wheal size of 3 mm or greater.

New Desensitization Protocol

We designed a practical new 11-step protocol in which the amount of oxaliplatin infused is similar to that used in the classic desensitization protocol [17]. Four bags containing different concentrations of oxaliplatin (1:1, 1:10, 1:100, 1:1000) were prepared as per the instruction manual. We first prepared one 500-mL bag containing 1:1 crude solution

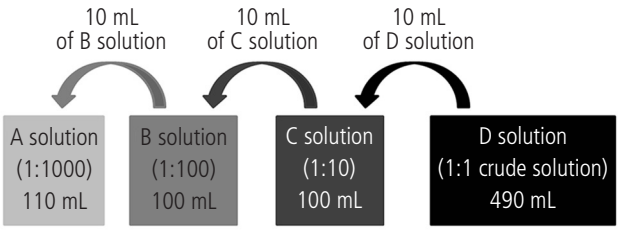

Figure 1. Process for preparing 4 bag solutions for the new practical oxaliplatin desensitization protocol.

(D solution) and three 100-mL bags containing 5% dextrose solution (A–C solutions). The D solution is used when patients receive platinum-based chemotherapy from the beginning of the chemotherapy regimen. The concentration of oxaliplatin is usually calculated using the patient's body surface area (BSA). We infused 10 mL of D solution into one 100-mL bag (C solution), at which point the C solution was diluted at a ratio of 1:10 of the D solution. We infused 10 mL of C solution into another 100-mL bag (B solution), and the B solution was diluted at a ratio of 1:100 of the D solution. Finally, the A solution (1:1000) was created by infusing 10 mL of the B solution into another 100-mL solution (Figure 1). We infused the 4 bags by order of concentration (A, B, C, and D, respectively). Rate of infusion was adjusted approximately every 15 minutes, from an initial rate of 60 mL/h to 120 mL/h or 240 mL/h. The last step of the classic 12-step protocol was omitted because the literature shows this step to be associated with an increased risk of IHSRs [17]. The final step of the newly designed 11-step protocol, which lasted 237.5 minutes at the 120 mL/h infusion rate, was carefully performed and monitored by an allergist (Table 1).

Table 1. New Practical Oxaliplatin Desensitization Protocol

Step	Solution	Rate (mL/h)	Time (min)	Volume Infused per Step (mL)	Fold Increase per Step
1	A solution (1:1000)	60	15	15	-
2		120	15	30	2
3		240	16.25	65	2
4	B solution (1:100)	60	15	15	2.5
5		120	15	30	2
6		240	13.75	55	2
7	C solution (1:10)	60	15	15	2.5
8		120	15	30	2
9		240	13.75	55	2
10	D solution (1:1 crude solution)	60	15	15	2.5
11		120	237.5	475	2
Total			383.25	800	

Volumetric Infusion Pump

We used a DI-2000 volumetric infusion pump (DAIWHA Corp., LTD.) to ensure accurate infusion rates and volumes. Infusion rate and volume can be established by inputting a number into the blank spaces on the device. When the assigned target volume is reached, an alarm sounds. For example, we input 60 into the space for rate adjustment and 15 into the space for volume adjustment before beginning to infuse solution A. Accordingly, this solution is infused at a rate of 60 mL/h until the infused volume of 15 mL is reached at 15 minutes. When the alarm sounds, we input 120 and 30 into the blank spaces for rate and volume, respectively. The solution is then infused at 120 mL/h for 15 minutes until a volume of 30 mL is reached. Following this procedure, four bags were regularly infused at an exact rate and volume.

IHSRs

IHSRs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 1 reactions involve transient flushing or rash and drug-related fever of under 38°C (<100.4°F) and do not require intervention; grade 2 reactions require intervention or interruption of infusion, prompt response for symptomatic treatment, and prophylactic medications for 24 hours or less; grade 3 reactions involve prolonged IHSRs, with recurrence of symptoms following initial improvement and hospitalization for clinical sequelae; grade 4 reactions have life-threatening consequences and require urgent intervention; and grade 5 reactions result in death [19]. We defined a mild reaction as grades 1–2 and a severe reaction as grades 3–5.

Ethics

This study was approved by the institutional review board at the Severance Hospital, Yonsei University Health System (approval number: 4-2014-0422). Before participation in the study, written informed consent was obtained from all participants.

Statistical Analysis

We determined ORs using logistic regression analysis in SPSS version 18.0. We first conducted univariate logistic regression analysis, followed by multiple logistic regression analysis using variables with a significant OR in the univariate analysis. Cross-correlation analysis was performed using χ^2 tests to analyze the correlation between the number of chemotherapy cycles and IHSRs. We considered a P value of less than .05 to be significant. Mean values are expressed as mean (SD).

Results

Baseline Characteristics and Clinical Manifestations of Oxaliplatin-Induced IHSRs in 271 Patients

There were slightly more women (56.3%) in the sample. The mean (SD) age and BSA were 58.1 (11.1) years and 1.6 (0.17) m^2. The most common underlying disease was colorectal

cancer (65.2%), followed by stomach cancer (24.8%), and pancreatic cancer (6.3%). The mean infused chemotherapy dose, which was adjusted to BSA, was 91.4 (18.4) mg/m^2. The mean number of infusion cycles was 9.8 (4.3). Most individuals who received oxaliplatin were being treated with FOLFOX chemotherapy.

Oxaliplatin-induced IHSRs occurred in 45 (16.7%) of the 271 patients. The most common clinical manifestations were cutaneous symptoms, including pruritus, rash, and urticaria (46.7%). Respiratory symptoms (chest tightness and dyspnea) and general symptoms (fever and myalgia) were also common (42.2% each). Cardiovascular symptoms, rhinorrhea, and neurologic symptoms were rare (Table 2).

Table 2. Baseline Characteristics and Clinical Manifestations

	Patients (n=271)	No. (%)
Sex	Male	118 (43.7)
	Female	152 (56.3)
Diagnosis	Colorectal cancer	176 (65.2)
	Stomach cancer	67 (24.8)
	Pancreatic cancer	17 (6.3)
	Ampulla of Vater cancer	6 (2.2)
	Appendiceal cancer	2 (0.7)
	Duodenal cancer	1 (0.4)
	Primary unknown cancer	1 (0.4)
Chemotherapy regimen	FOLFOX[a]	225 (83.3)
	Xelox[b]	45 (16.7)
Clinical manifestations	Cutaneous	21 (46.7)
	Respiratory	19 (42.2)
	General	19 (42.2)
	Cardiovascular	2 (4.4)
	Rhinorrhea	2 (4.4)
	Neurologic	1 (2.2)

[a]FOLFOX: oxaliplatin 85 mg/m^2 intravenous infusion (IVF), fluorouracil 400 mg/m^2 intravenous bolus, fluorouracil 2400 mg/m^2 IVF, leucovorin 200 mg/m^2 IVF
[b]Xelox: oxaliplatin 130 mg/m^2 IVF, capecitabine 1500 mg/m^2 orally divided by 2 daily doses for 14 days.

IHSRs

Figure 2 shows a flowchart of IHSRs. Of the 45 patients who experienced these reactions, 34 patients, 9 patients, and 2 patients experienced grade 1, 2, and 3 reactions during their first IHSR, respectively. Thirty-two of the 34 patients who experienced a grade 1 reaction were re-exposed to oxaliplatin. Of these, 19 patients experienced a second grade 1 reaction during subsequent chemotherapy and 1 patient experienced a grade 2 reaction. Seven of the 9 patients who experienced a grade 2 reaction during the first IHSR were re-exposed. Three experienced another grade 2 reaction during additional chemotherapy. The 2 patients who experienced a grade 3 reaction during the first IHSR stopped chemotherapy as a direct result. Consequently, the recurrence rate of IHSRs was 59.0% (23 patients with IHSR recurrence/39 patients re-exposed to oxaliplatin).

Of the 19 patients who experienced a grade 1 IHSR during re-exposure, 7 experienced at least one other grade 1 reaction, 1 experienced a grade 2 reaction, and 1 experienced a grade 3 reaction during subsequent chemotherapy. Of the 4 patients who experienced a grade 2 IHSR during re-exposure, 1 patient experienced another reaction of equal severity and 1 stopped chemotherapy due to recurrent IHSRs. Of the 10 patients who experienced a third oxaliplatin IHSR, 2 experienced additional IHSRs during further chemotherapy. These 2 patients and an additional patient who experienced a grade 3 reaction during the third IHSR stopped chemotherapy. Of the 39 patients who experienced an IHSR and were required to have additional chemotherapy, 6 patients did not continue the chemotherapy

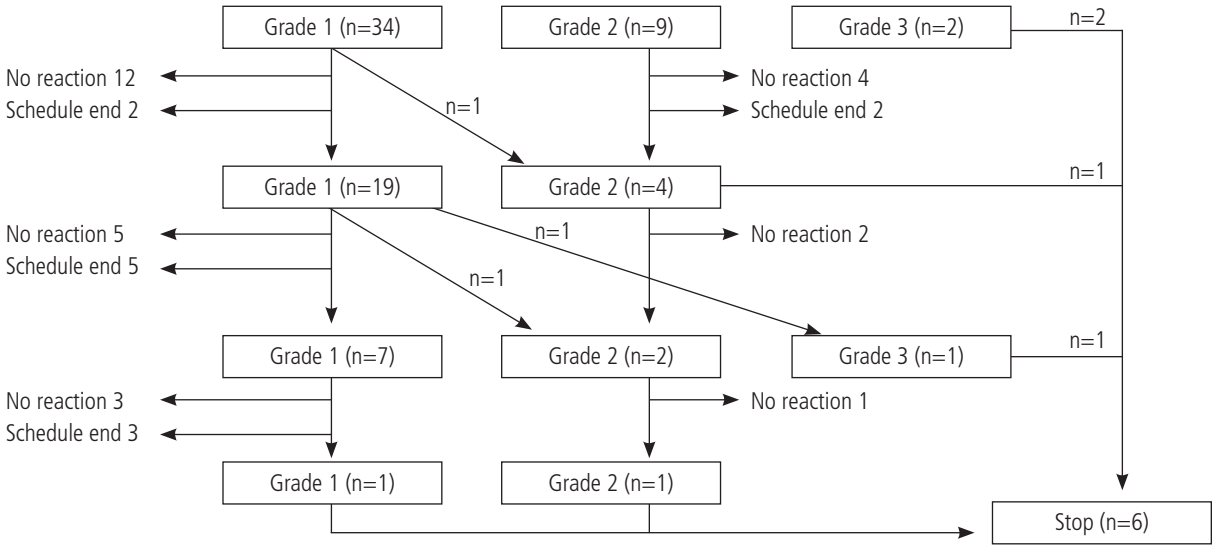

Figure 2. Flowchart showing management and outcomes of immediate hypersensitivity reactions.

Table 3. ORs for Immediate Hypersensitivity Reactions Induced by Oxaliplatin

	OR (95% CI)	*P* Value	Adjusted OR (95% CI)	*P* Value
Sex (female)	0.592 (0.367-0.956)	.032	0.713 (0.393-1.292)	.265
Body surface area (m^2)	5.651 (1.479-21.585)	.011	0.050 (0.000-24.964)	.345
Relevant cycle of chemotherapy	1.132 (1.085-1.181)	<.001	0.996 (0.805-1.233)	.970
Infusion dose (mg/m^2)	0.972 (0.958-0.986)	<.001	0.895 (0.783-1.023)	.104
Infusion amount (mg)	0.991 (0.983-0.998)	.012	1.050 (0.972-1.135)	.215
Total accumulated amount (mg)	1.001 (1.000-1.001)	<.001	1.001 (0.999-1.002)	.276

regimen after this first reaction (discontinuation rate due to oxaliplatin IHSR, 15.4%). However, the remaining 33 patients (84.6%) continued chemotherapy, regardless of the high risk of urticaria, angioedema, or anaphylaxis due to IHSR recurrence.

ORs for IHSRs Induced by Oxaliplatin

Based on the logistic regression analysis, type of chemotherapy regimen (*P*=.281) and total number of cycles administered (*P*=.762) were not risk factors for oxaliplatin-induced IHSRs. Significant ORs, however, were observed for sex, BSA, current cycle of chemotherapy, infusion dose (mg/m^2), infusion amount (mg), and total accumulated amount (mg). The adjusted ORs for these variables, however, were not statistically significant (Table 3). Nonetheless, the cross-correlation analysis showed that number of chemotherapy cycles was significantly correlated with the occurrence of IHSRs (*P*<.001).

Chemotherapy Cycle at Moment of First IHSR

IHSRs occurred approximately during the third cycle and after the sixth cycle (Figure 3). Of the 5 patients who experienced their first IHSR during the third cycle, 2 patients developed fever, and the others experienced throat tightness, rash, and urticaria. After the sixth cycle, the patients experienced, to diverse extents, fever, urticaria, pruritus, dyspnea, and anaphylaxis (Table 4).

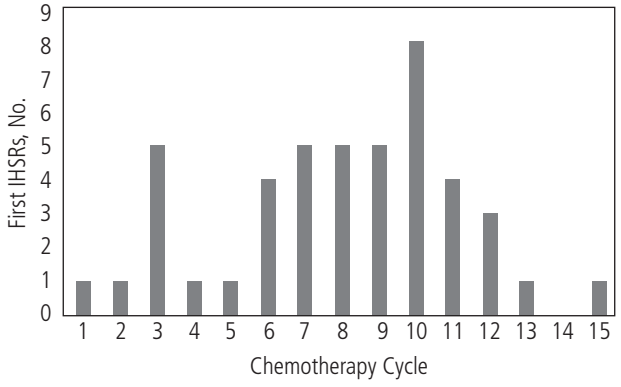

Figure 3. Number of chemotherapy cycles when first immediate hypersensitivity reaction (IHSR) to oxaliplatin occurred.

Clinical Characteristics of Patients Who Underwent Desensitization

We used our new desensitization protocol 32 times in 12 prospectively enrolled patients who had experienced an IHSR to platinum-based chemotherapy. Their mean (SD) age was 51.6 (8.4) years. The mean number of cycles preceding the first IHSR

Table 4. Symptoms of IHSRs According to Cycle During Which the First IHSR Occurred

Cycle When First IHSR Occurred	Symptom	Cycle When First IHSR Occurred	Symptom
1	Throat tightness	9	Fever
2	Pruritus	9	Fever
3	Fever	9	Urticaria
3	Fever	9	Urticaria
3	Throat tightness	9	Urticaria
3	Rash	10	Fever
3	Urticaria	10	Fever
4	Chest tightness	10	Fever
5	Rhinorrhea	10	Fever
6	Hypertension	10	Rhinorrhea
6	Fever	10	Pruritus
6	Urticaria	10	Urticaria
6	Urticaria	10	Urticaria
7	Fever	11	Fever
7	Pruritus	11	Fever
7	Pruritus	11	Pruritus
7	Urticaria	11	Dyspnea
7	Anaphylaxis	12	Fever
8	Fever	12	Fever
8	Fever	12	Rash
8	Pruritus	13	Fever
8	Rash	15	Urticaria
8	Urticaria		

Abbreviation: IHSR, immediate hypersensitivity reaction.

was 6.5 (6.7), and the mean number of cycles before the patients first underwent desensitization was 9.4 (7.1). Most patients had colorectal cancer (42.7%) or stomach cancer (42.7%). One of the patients with stomach cancer and one with cervical cancer received cisplatin-based chemotherapy, and the rest received oxaliplatin-based chemotherapy. Half of the patients had experienced severe IHSRs, including anaphylactic shock. The most common type of IHSR consisted of general symptoms, such as fever, hypertension, and anaphylaxis. Many of the patients also experienced cutaneous symptoms (pruritus, urticaria, and rash, 50.0%) and respiratory symptoms (chest tightness, wheezing, dyspnea, 42.7%), and some patients experienced tachycardia, nausea, and a tingling sensation (Table 5).

Results of Intradermal Skin Tests and Responses to the Newly Designed Desensitization Protocol

All patients successfully underwent the newly designed desensitization protocol including the full dose of chemotherapy. There were no complications or deaths. Almost all of the patients (87.5%) experienced either a mild adverse reaction or no reaction. Mild reactions recurred in 42.8% of all cases. All 9 patients who had a mild reaction or no reaction showed positive results on the skin test. Of the 5 patients who experienced a mild reaction, 3 experienced symptoms during the 11th step, which consisted of a 1:1 concentration of the D solution at 120 mL/h. One patient experienced symptoms during the 10th step, which consisted of a 1:1 concentration of the D solution at 60 mL/h. Only 1 patient experienced symptoms immediately after the skin test. However, after treatment with dexamethasone and pheniramine, their symptoms were relieved. Patient 9 experienced urticaria, chest tightness, nausea, and dizziness immediately after the skin test. During desensitization, patient 9 developed some breakthrough symptoms; treatment with dexamethasone and pheniramine, followed by a 30-minute pause, helped to improve tolerability and allowed the desensitization protocol to be completed (Table 6).

Only 4 of the IHSRs (12.5%), in 3 patients, were severe. While the patients had no urticaria or pruritus, they did experience fever or hypertension with a mild rash and flushing. The fever and/or hypertension occurred immediately after oxaliplatin infusion, and the symptoms could only be explained by this infusion. The 3 patients showed negative results on the skin test. They experienced their first IHSR during the first to third cycle of chemotherapy, and chose not to undergo additional steps of the desensitization protocol because they felt that it was not effective. They finally switched to a platinum-free chemotherapy regimen (Table 6).

Table 5. Clinical Characteristics of 12 Patients Enrolled in Prospective Desensitization Study

Variables		Mean (SD)
Age, y		51.6 (8.4)
Cycle when first IHSR occurred		6.5 (6.7)
Cycle when desensitization protocol was first administered		9.4 (7.1)
Variables		**No. (%) of Patients**
Underlying disease	Colorectal cancer	5 (42.7)
	Stomach cancer	5 (42.7)
	Gallbladder cancer	1 (8.3)
	Cervical cancer	1 (8.3)
Type of chemotherapy	Oxaliplatin	10 (83.3)
	Cisplatin	2 (16.7)
Grade of IHSR	Mild	6 (50.0)
	Severe	6 (50.0)
Type of IHSR	General	8 (66.7)
	Cutaneous	6 (50.0)
	Respiratory	5 (42.7)
	Cardiologic	2 (16.7)
	Gastrointestinal	1 (8.3)
	Neurologic	1 (8.3)
Total		12 (100.0)

Abbreviation: IHSR, immediate hypersensitivity reaction.

Discussion

Many studies have investigated the predictive factors for IHSR. In Japan, one study revealed that serum lactate dehydrogenase (LDH) levels at the beginning of chemotherapy might predict IHSRs to oxaliplatin [20], and a Korean study suggested that the amount of dexamethasone used as premedication could predict IHSRs [21]. Further studies, however, are needed to confirm the reliability of these factors. In our study, LDH was not routinely measured at the start of chemotherapy. All the individuals received premedication including dexamethasone and chlorpheniramine immediately before the infusion of oxaliplatin. Our study did not find that any of these newly reported factors were predictive of oxaliplatin IHSR, supporting the findings of other studies [6]. Coinciding with many previous studies, in our series, only number of chemotherapy cycles was significantly correlated with the occurrence of IHSRs.

First IHSRs to oxaliplatin tend to occur during the seventh to ninth infusion [6,8-12], although recent studies have shown that they can occur earlier [10,13]. In our study, we observed 2 peaks of occurrence for the first IHSR: one around the third cycle and another around the sixth cycle. These data suggest that a significant portion of oxaliplatin IHSRs can occur earlier than previously reported. We analyzed the symptoms of IHSRs according to the cycle administered, but found no significant differences between early (around the third cycle) and late (seventh-eight cycles) occurrences.

IHSRs are generally divided into 2 types: true allergic IHSRs that usually involve IgE-mediated (type 1) hypersensitivity, and pseudoallergic or idiosyncratic IHSRs that are not associated with IgE. Some drugs, such as radiocontrast media, are considered to result in both types of IHSR [22]. Skin tests are a diagnostic tool for IgE-mediated IHSRs. A negative skin test in certain IHSR patients might suggest that IHSRs are non-IgE-mediated reactions. However, the sensitivity rates of skin tests to oxaliplatin vary from 26% to 100% [9,23,24]. Furthermore, the ImmunoCAP system, which measures specific IgE in oxaliplatin-reactive patients, has a sensitivity of 38% to 54% [23]. In our study, the rate of positive skin

Table 6. Results of Intradermal Skin Test and Responses to the Newly Designed Oxaliplatin Desensitization Protocol

Patient	Type of Chemotherapy	Cycle When First IHSR Occurred	Main Clinical Manifestation	No. of Desensitizations	Cycle	Skin Test	Results	Protocol Step When First IHSR Occurred
1	Oxaliplatin	11	Anaphylactic shock	1	13	+	Mild reaction	Step 11
				2	14	+	No reaction	
				3	15	+	No reaction	
				4	16	+	No reaction	
2	Cisplatin	25	Anaphylactic shock	1	26	+	Mild reaction	Step 11
				2	27	+	No reaction	
				3	28	+	No reaction	
3	Oxaliplatin	9	Anaphylaxis	1	12	+	No reaction	
4	Oxaliplatin	3	Anaphylaxis	1	3	+	No reaction	
				2	4	+	No reaction	
				3	5	+	No reaction	
				4	6	+	No reaction	
5	Oxaliplatin	6	Fever, urticaria	1	12	+	Mild reaction	Step 11
				2	13	+	Mild reaction	Step 11
				3	14	+	Mild reaction	Step 11
				4	15	+	Mild reaction	Step 11
6	Oxaliplatin	7	Fever	1	11	+	No reaction	
				2	12	+	No reaction	
7	Oxaliplatin	1	Fever	1	7	+	No reaction	
				2	8	+	No reaction	
8	Oxaliplatin	7	Fever, hypertension, urticaria	1	16	+	Mild reaction	Step 10
				2	17	+	Mild reaction	Step 10
				3	18	+	Mild reaction	Step 10
				4	19	+	Mild reaction	Step 10
				5	20	+	Mild reaction	Step 11
9	Cisplatin	2	Anaphylactic shock	1	3	+	Mild reaction	Skin test
				2	4	+	Mild reaction	Skin test
				3	5	+	Mild reaction	Skin test
10	Oxaliplatin	2	Hypertension, fever	1	4	-	Severe reaction	Step 11
11	Oxaliplatin	1	Fever	1	3	-	Severe reaction	Step 11
				2	4	-	Severe reaction	Step 11
12	Oxaliplatin	3	Fever	1	4	-	Severe reaction	Step 10

tests in the 12 patients who underwent the desensitization protocol was 65%, but the nonresponders to this protocol had negative skin test responses, suggesting the involvement of a non-IgE mediated mechanism. There are 2 likely types of mechanisms in oxaliplatin-induced IHSRs: IgE-mediated and non-IgE-mediated. Negative skin test results may indicate non-IgE-mediated IHSRs and consequently a lower likelihood of the desensitization protocol being effective. Further studies with larger samples are needed to confirm the validity of skin tests for predicting the success of this desensitization protocol. We did not evaluate the level of specific IgE to oxaliplatin. For ELISA analysis, conjugation of oxaliplatin with a carrier protein is needed, but the in vitro conjugation process is not easy due to the chemical structure of oxaliplatin.

The prevalence of IHSRs to oxaliplatin is so high that many patients decide to stop oxaliplatin-based chemotherapy and switch to another, less effective, agent. Desensitization is an ideal strategy for maintaining the safety and effectiveness of oxaliplatin-based chemotherapy. From a practical standpoint, the well-known classic desensitization protocol has several limitations. First, the preparation of solutions is impractical, and the calculation of formulas for preparing the 3-bag solution are complicated and time-consuming. These challenges can cause errors during solution preparation. Second, the recommended infusion rate and volume for 15 minutes are also impractical. Based on the classic desensitization protocol, 0.5 mL of the first solution should be infused for 15 minutes, but this tiny volume can remain in the line or syringe needle for this time, making it impossible to ensure that the exact amount of solution is infused into the patient over the established 15 minutes. Third, the infusion rate varies from 2 mL/h to 80 mL/h according to the solution concentration. Such variations might cause confusion among health professionals and lead to errors.

The newly designed desensitization protocol is suitable for real clinical practice. Formula calculations are not difficult, and the only reagent that needs to be prepared is the crude

solution, which is the solution typically used in the standard cycle. Using another three 100-mL bags and syringes, it is easy to prepare solutions containing 1:10, 1:100, and 1:1000 concentrations of oxaliplatin. Once the bags are prepared, health professionals can infuse the solution using a volumetric infusion pump, which automatically adjusts infusion rate and volume. Nursing staff can simply input the established rates of 60 mL/h to 120 mL/h and 240 mL/h, in that order, into the blank space for infusion rate, and then add the established volumes of 15 mL and 30 mL. The last number for infusion volume can be left empty, meaning that all the solution will be infused. If the machine reaches the target volume or infuses to the end, an alarm will sound. After infusion of solution A, solution B should be infused, in the same order as above, from 60 mL/h to 120 mL/h and 240 mL/h. Solutions C and D are then infused, also in the same order. Note that solution D should not be infused at 240 mL/h. The maximum infusion rate for this solution is 120 mL/h, which is about half of the normal infusion rate of the original FOLFOX regimen in nonsensitized patients.

This new protocol can be used easily and safely in routine clinical practice. It is not only feasible but also reduces the potential for medication errors. The success rate of this new protocol was high, and it was safely administered to all patients. Furthermore, there were no errors during its use in 7 patients. The protocol, however, has yet to be applied on a larger scale. Therefore, large-scale studies should be conducted to evaluate the efficacy and safety of this new protocol.

A considerable number of patients experience IHSRs to oxaliplatin, and the decision whether or not to continue with what is an effective regimen poses a dilemma. Many hospitals hesitate to use the classic desensitization protocol because of the duration and cost of the procedure and a lack of health professionals trained in its use. We suggest that this new practical desensitization protocol will prove useful to patients with oxaliplatin-induced IHSRs in real clinical practice.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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