RESEARCH COMMUNICATION

Hypersensitivity Reactions to Oxaliplatin: Clinical Features and Risk Factors in Koreans

Mi-Yeong Kim[1,2], Sung-Yoon Kang[1,2], Suh-Young Lee[1,2], Min-Suk Yang[1,2], Min-Hye Kim[1,2], Woo-Jung Song[1,2,3], Sae-Hoon Kim[1,2,3], You Jung Kim[1,2,3], Keun-Wook Lee[1,2,3], Sang-Heon Cho[1,2], Kyung-Up Min[1,2], Jong Seok Lee[1,2,3], Jee Hyun Kim[1,2,3], Yoon-Seok Chang[1,2,3]*

Abstract

Background and Aim: Oxaliplatin hypersensitivity is a well-known adverse reaction but the prevalence varies and data for frequency and clinical features have not been reported for Korea. Here we evaluates the prevalence and risk factors for hypersensitivity reactions to oxaliplatin after chemotherapy. Methods: Clinical information on all patients treated with oxaliplatin was retrospectively reviewed in electronic medical records between August 2009 and July 2010 in Seoul National University Bundang Hospital. Patients who experienced hypersensitivity reactions to oxaliplatin were compared with those who did not. Results: A total of 393 patients received oxaliplatin, with 42 (10.7%) experiencing hypersensitivity reactions including three cases of anaphylaxis. Median cycle of the first hypersensitivity reaction was 8. Reactions correlated with lower dexamethasone doses. Other variables were not significant. Conclusions: The prevalence of hypersensitivity reactions was 10.7%, symptoms being mostly mild and cutaneous. Lower dexamethasone doses could be a predictor for hypersensitivity reactions to oxaliplatin.

Key words: Oxaliplatin - hypersensitivity - drug hypersensitivity - electronic health records

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Introduction

Oxaliplatin is a third generation platinum agent with a 1, 2-diaminocyclohexane carrier ligand and an oxalate leaving group (Kelland, 2007). Its anti-neoplastic effects occur via generation of DNA adducts into intra- or interstrand guanine residues, which lead to DNA kinks and strand breaks, as well as inhibition of DNA polymerase and DNA synthesis. These effects lead to cell cycle arrest and apoptosis (Faivre et al., 2003). Oxaliplatin has shown activity in a wide variety of tumor types, including colorectal, pancreatic, biliary, gastroesophageal, and gynecologic malignancies (Gowda et al., 2004). In recent years, oxaliplatin has been extensively used, which led to an increased prevalence of oxaliplatin related hypersensitivity reactions (Brandi et al., 2003; Thomas et al., 2003; Gowda et al., 2004; Maindrault-Goebel et al., 2005; Siu et al., 2006; Lee et al., 2007).

The reported prevalence was variable. The previous study, the MOSAIC trial, a large randomized multi-institution randomized trial in which over 1,100 patients received 5-fluouracil with oxaliplatin for colorectal cancer in the adjuvant setting, reported a 10.3% prevalence of oxaliplatin hypersensitivity reactions, which were one of the major reactions for discontinuing treatment (Andre et al., 2004). In other studies, Shao et al., (2010) reported a 12.7% prevalence, and Polyzos et al., (2009) reported a 25% prevalence of oxaliplatin hypersensitivity. Manifestations were also diverse. Polyzos et al., (2010) clinically distinguished the reactions in mild and severe. Mild reactions occurred in 195 (63%) patients manifesting with itching and small area erythema, and severe reactions occurred in 113 (37%) patients manifesting with diffuse erythema, facial swelling, chest tightness, bronchospasm and changes in blood pressure. Incidence of each reaction was not reported. Kim et al., (2009) reported that the most common events were flushing (15 patients, 51.7%), urticaria (15 patients, 51.7%) and dyspnea without bronchospasm (7 patients, 24.1%). Shao et al., (2010) reported that most common events were cutaneous symtoms (61 patients, 70.9%).

There are few reports on the risk factors of oxaliplatin hypersensitivity (Lee et al., 2006; Kim et al., 2009;

*[1]Department of Internal Medicine, Seoul National University College of Medicine, [2]Institute of Allergy and Clinical Immunology, Seoul National University Medical Research Center, Seoul, [3]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea *For correspondence: addchang@snu.ac.kr*

Polyzos et al., 2009; Shao et al., 2010; Kidera et al., 2011). Kim et al. (2009) investigated risk factors of hypersensitivity reactions, and younger age, female, and with use of oxaliplatin as salvage therapy were suggested as potential risk factors. Shao et al. (2010) reported that the prevalence of hypersensitivity reactions increased with each repeated infusion, and higher oxaliplatin dose per infusion was an independent risk factor. However, there was not a consistently confirmed risk factor, and we could not yet apply these risk factors in clinical practice. In addition, the incidence and clinical features has not been reported in Korea. Only a few cases of hypersensitivity reactions were reported. Lee et al., (2006) reported on two patients who developed hypersensitivity reactions to oxaliplatin. One patient experienced anaphylaxis ten minutes after oxaliplatin administration at the 7th cycle, and recovered after injection of intravenous hydrocortisone and volume expansion. Another one experienced fever and chilling about four hours after oxaliplatin administration at 4th cycle, and similar symptoms were represented after readministration at next cycle. We should understand prevalence, clinical feature, and risk factors of hypersensitivity reactions to oxaliplatin, and carefully check whether hypersensitivity reactions including anaphylaxis occur.

In this retrospective study, we analyzed the prevalence, presentation, severity, and risk factors of hypersensitivity reactions to oxaliplatin. This is the first report on the prevalence and risk factors of oxaliplatin hypersensitivity in Korea.

Materials and Methods

Patients and study protocol

We retrospectively searched the data base of the electronic medical records from Seoul National University Bundang Hospital in Korea. All patients who had received at least one dose of oxaliplatin at inpatient or outpatient department during the period from August 2009 to July 2010 were enrolled. Medical records during oxaliplatin infusion were reviewed by physician retrospectively. We reviewed baseline characteristics, such as age, sex, presence of preexisting allergies and cancer diagnosis. In addition, data on dose, rate and interval of oxaliplatin administered, total number of oxaliplatin courses, premedication, purpose of chemotherapy and regimen of chemotherapy were collected. Hypersensitivity reactions were classified into cutaneous, digestive, respiratory, generalized symptoms, dizziness, tingling sense, chest discomfort and consciousness change. In addition, data on the grade of hypersensitivity, the time elapsed before onset of the reaction and the cycle of first hypersensitivity was collected. The severity of these reaction was evaluated according to the National Cancer Institute Common Toxicity Criteria version 2.0 (CTC) and Common Terminology Criteria for Adverse Events version 3.0 (CTCAE) (Trotti et al., 2003). Grade 0 means no adverse event or within normal limits, and grade 1 means mild adverse events (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance). Grade 2 means moderate adverse events (minimal intervention; local intervention; noninvasive intervention [packing, cautery]), and grade 3 means severe and undesirable adverse events (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation). Grade 4 means life-threatening or disabling adverse events (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, and sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation), and grade 5 means fatal adverse events.

This study was approved by institutional review board in Seoul National University Bundang Hospital (IRB No. B-1103/124-110).

Statistical methods

Statistical analyses were performed with SPSS version 18.0. We carried out statistical analysis using the logistic regression for risk factor evaluation. First, we carried out statistical analysis using the univariable logistic regression, and factors which showed significant difference and factors proposed in previous studied (Polyzos, 2009; Kim, 2009; Shao, 2010; Santini, 2001), such as purpose of chemotherapy, oxaliplatin infusion dose, and dexamethasone dose were adjusted. Results were considered significant when two-sided p values < 0.05.

Results

Study subjects

A total of 393 patients were enrolled in this study. Their baseline characteristics are listed in Table 1. The mean age was 59.2 (±12.2) years, and the number of male was 213 (54.2%). Most patients (90.3%) had no prior history of allergic reactions. Only 38 patients had prior allergic reactions, and most frequent reaction was hypersensitivity to medications including radio-contrast dye. Colorectal cancer (70.5%) was the most common type of cancer, with the remainder consisting of gastric cancer (26.5%), pancreas cancer (1.0%), bile duct cancer (0.5%), breast cancer, peritoneum cancer, liver cancer, and small bowel cancer. Oxalipatin was infused over two hours and combined either with fluorouracil and folinic acid at doses from 50 to 130 mg/m2 (modified FOLFOX-6 (75.1%), FOLFOX-4 (2.8%), and FOLFOX-6 (0.5%)), while in several cases, oxaliplatin was given in combination with gemcitabine (XELOX (21.1%)). Some patients of colorectal cancer were received these regimens with bevacizumab, and

Table 1. Baseline Characteristics

Subjects (total =393)		N (%)
Age (yr)*		59.2 (47.0-71.4)
Sex, male		213 (54.2)
Prior history of Allergy, n=38	Medication	33 (86.8)
	Radio-contrast	22 (66.7)
	Others	11 (33.3)
	Food	3 (7.9)
	Others	2 (5.3)
Type of cancer	Colorectal	277 (70.5)
	Gastric	104 (26.5)
	Pancreatic	4 (1.0)
	Biliary tract	2 (0.5)
	Others	6 (1.5)
Infusion dose (mg/m2)*		91.7 (74.6-108.8)
Infusion time (min)†		120
Total infusion course*		8.5 (4.6-12.5)
Interval of chemotherapy cycle	Biweekly	293 (74.6)
	Triweekly	99 (25.2)
	Others	1 (0.3)
Purpose of chemotherapy	Palliative	232 (59.0)
	Adjuvant	161 (41.0)
	Neoadjuvant	0 (0)
Chemotherapy regimen	Modified FOLFOX-6	295 (75.1)
	XELOX	83 (21.1)
	FOLFOX-4	11 (2.8)
	FOLFOX-6	2 (0.5)
	Others	2 (0.5)
Premedication	Serotonin (5-HT3) antagonist	393 (100)
	Dexamethasone	384 (97.7)
	Histamine-2 (H2) antagonist	338 (86.0)
	Other steroid	1 (0.3)
Dexamethasone (mg)	<20	248 (63.1)
	≥20	137 (34.9)
	Nill	8 (2.0)

* data presented as mean (95% confidence interval); † Durations of all patient were same

some patients of gastric cancer were received them with sunitinib. Oxaliplatin was given as a biweekly regimen in 74.6% of patients, and as a triweekly regimen in 25.2% of patients. Fifty-nine percent of them received oxaliplatin for palliative therapy. The mean of total infusion courses was 8.5 (range, 1-44). All patients received serotonin antagonist for prophylaxis to emesis, and most of them also received histamine-2 antagonist and dexamethasone as premedication. Dose of dexamethasone as protocol of our hospital were 12mg in first day and each 4mg in second and third days. However, these dose could be adjusted according to medical condition of patients by clinician.

Prevalence and clinical manifestations of oxaliplatin-induced hypersensitivity

Forty-two patients had hypersensitivity reactions to oxaliplatin, for prevalence rate of 10.7%. The manifestation of hypersensitivity is shown in Table 2. Most common events were rash (25 patients) and nausea (6 patients). The severity of reactions varied from mild to severe. In thirty-seven (88%) of forty-two patients, the

Table 2. Manifestations of Oxaliplatin-induced Hypersensitivity Reactions

Subjects (total=42)			N (%)
Symptom	Cutaneous		30 (71.4)
		Rash	25 (59.2)
		Urticaria	5 (11.9)
	Digestive		12 (28.6)
		Nausea	6 (14.3)
		Vomiting	3 (7.1)
		Others	3 (7.1)
	Neurologic		10 (23.8)
		Dizziness	5 (11.9)
		Tingling sense	3 (7.1)
		Consciousness change	2 (4.8)
	Respiratory		8 (19.1)
		Dyspnea	5 (11.9)
		Chest discomfort	3 (7.1)
		Wheezing	2 (4.8)
		Cough	1 (2.4)
	Generalized		5 (11.9)
		Sweating	5 (11.9)
		Chills	1 (2.4)
	Cardiovascular		4 (9.5)
		Hypotension	4 (9.5)
Grade of severity		1-2	37 (88.1)
		3-5	5 (11.9)
Time elapsed before onset of the reaction (min)*			40 (10-120)
Cycle at the first hypersensitivity reaction†			8 (1-12)

* data from 11 patients and presented as mean (minimum-maximum); † data presented as median (minimum-maximum)

symptoms were grade 1 or 2. Grade 3 events included hypotension in 4 patients, diarrhea in 2 patients, and consciousness change in 1 patient. Three patients of them experienced anaphylaxis. They complained of wheezing, dizziness, abdominal pain or loss of consciousness with hypotension. There was no case of death. The first hypersensitivity reactions developed after a median of eight infusions of oxaliplatin (range 1-12) (Figure 1). The time elapsed before the onset of the reaction (min) was recorded in eleven patients, and the mean time of onset from start of infusion was 40 minutes (range, 10-120).

Clinical course of the patients who experienced hypersensitivity reactions

The patients with hypersensitivity reactions to oxaliplatin were treated with intravenous medications. They included histamine-receptor 1 antagonist (29 patients), hydrocortisone (12 patients), and others. Sixteen patients of them stopped oxaliplatin infusion and were observed until their symptoms improved. Ten patients had very mild symptoms, and they were just observed without medication.

At the next cycle of chemotherapy, patients who had experienced oxaliplatin-related hypersensitivity reactions were treated different treatment plans according to the severity of reactions, the purpose of chemotherapy and remained cycles which were planned (Table 3). Thirty patients (71%) received subsequent courses of oxaliplatin administration by using additional antihistamine

Table 3. Clinical Decision at the Next Cycle of Chemotherapy after the Occurrence of Oxaliplatin-Induced Hypersensitivity Reactions (n=42)

	N (%)
Same regimen with prophylaxis	30 (71.0)
Same regimen except oxaliplatin	6 (14.2)
Same regimen with desensitization	3 (7.1)
Stopped chemotherapy	3 (7.1)

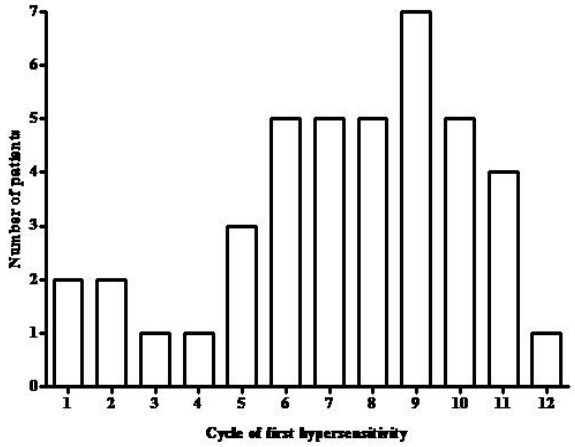

Figure 1. Cycels of Therapy when First Hypersensitivity Reactions Occurred during Oxaliplatin Infusion

drugs and hydrocortisone as premedications before chemotherapy. Six patients (14.2%) received their previous chemotherapeutic regimens except oxaliplatin. Three patients received oxaliplatin with desensitization. Two patients of them could tolerate subsequent courses of oxaliplatin administration. For the remaining one patient, retreatment was not feasible because of severe urticaria and cough occurring after oxaliplatin administration.

Risk factors for oxaliplatin hypersensitivity reactions

To examine the potential risk factors for the development of hypersensitivity reactions, characteristics were analyzed by the multivariable logistic regression (Table 4). The patients who received more than 90 mg/m2 dose of oxaliplatin had less risk of oxaliplatin hypersensitivity (odd ratio (OR)=0.37, 95% confidence interval (CI) 0.16-0.86, p=0.021). The patients who received less than 20 mg dose of dexamethasone also had more risk of oxaliplatin hypersensitivity (OR=4.50, 95% CI 1.73-11.74, p=0.002). After adjusting age, sex, purpose of chemotherapy, oxaliplatin infusion dose and dexamethasone dose, lower dexamethsone dose was found to be the only significant risk factor of oxaliplatin hypersensitivity (OR=3.74, 95% CI 1.34-10.46, p=0.012). Age, sex, the purpose of chemotherapy and the dose of oxaliplatin infusion were not associated with oxaliplatin-induced hypersensitivity reactions.

Discussion

Oxaliplatin has been used extensively worldwide for treating colorectal cancer and other malignancies. Hypersensitivity reactions during oxaliplatin infusion are major problem associated with its use (Kidera et al., 2011). Hypersensitivity reactions can be the cause of discontinuation of oxaliplatin infusion. There have been limited reports on the characteristics and the risk factors of oxaliplatin-related hypersensitivity reactions, and adverse reactions would be important with extensive use of oxaliplatin (Kidera et al., 2011; Kim et al., 2009; Polyzos et al., 2009; Shao et al., 2010; Shibata et al., 2009). In addition, there is not perfect tool to predict oxaliplatin-related hypersensitivity reactions. Skin testing for oxaliplatin showed 75% to 80% accuracy in previous two studies (Garufi et al., 2003; Morgan et al., 1994), but the usefulness of skin testing remains an issue of controversy (Makrilia et al., 2010).

We present a retrospective study on oxaliplatin-related hypersensitivity reactions. The prevalence of hypersensitivity reactions was 10.7%, and this prevalence was consistent with previous studies with rate of 3.6%-25% (Andre et al., 2004; Brandi et al., 2003; Gowda et al., 2004; Maindrault-Goebel et al., 2005; Siu et al., 2006; Thomas et al., 2003). Most common events were cutaneous symptoms including rash and/or urticaria, and most symptoms were not severe: these results were also similar to results of previous studies (Shao et al., 2010). Hypersensitivity reactions developed after median eighth courses. In two patients (4.8%), the hypersensitivity reactions occurred at the first exposure and their symptoms were mild. It has been reported that all platinum compounds could induce allergic reactions (Polyzos et al., 2001; Zanotti

Table 4. Risk Factors of Oxaliplatin-induced Hypersensitivity Reactions

	Crude OR* (95% CI)	P value	Adjusted OR* (95% CI)	P value
Age < 65 years	1		1	
≥ 65 years	0.65 (0.32-1.31)	0.226	0.65 (0.31-1.36)	0.252
Sex female	1		1	
male	0.60 (.031-1.15)	0.121	0.68 (0.35-1.32)	0.248
Chemotherapy adjuvant	1		1	
palliative	0.74 (0.39-1.40)	0.355	1.41 (0.68-2.93)	0.354
Oxaliplatin infusion dose < 90 mg/m2	1		1	
≥ 90 mg/m2	0.37 (0.16-0.86)	0.021	0.50 (0.19-1.32)	0.160
Dexamethasone dose ≥ 20 mg	1		1	
< 20 mg	4.50 (1.73-11.74)	0.002	3.74 (1.34-10.46)	0.012

Adjusted factors: age, sex, purpose of chemotherapy, oxaliplatin infusion dose, and dexamathesone dose; *OR; odds ratio

et al., 2001; Basu et al., 2002; Koren et al., 2002). However, the exact mechanism of the allergy remains unclear, and the pathophysiology of oxaliplatin induced allergic reactions is also undetermined. The suggested mechanism was the type I hypersensitivity reaction mediated by immunoglobulin E with histamine release (Morgan et al., 1994 ; Koren et al., 2002). Leguy-Seguin et al. assessed the value of skin test with platinum salts including cisplatin, carboplatin, and oxaliplatin (Collet et al., 2007). Intradermal tests could be particularly indicated for the diagnosis of immediate hypersensitivity reactions. As other kinds of hypersensitivity mechanism, type II allergic reaction should be considered. There were a few cases of type II immunoallergic thrombocytopenia (Bajetta et al., 2010; Bautista et al., 2010; Mason and Rees, 2010). Pietrantonio et al. reported a case of acute immune-mediated thrombocytopenia due to oxaliplatin administration (Bajetta et al., 2010). The patients received adjuvant chemotherapy with oxaliplatin, 5-fluorouracil and leucovorin (FOLFOX-4), and experienced occasional and grade 1 epistaxis and gum bleeding during the last weeks of the eleventh administration. Immediately after last twelfth course of chemotherapy, the appearance of ecchymoses and petechial hemorrhages particularly on the face and extremities was noted, and during the next day the clinical conditions worsened rapidly, with the appearance of large subcutaneous hematomas. The patient started systemic corticosteroids, and the blood cell count returned to acceptable levels within 4 days. Some cases suggesting type III hypersensitivity reaction also have been reported (Petit-Laurent et al., 2000; Villee et al., 2010). Petit-Laurent et al. described the case of a 56-year-old woman who developed a generalized urticarial and pruritic rash 8 days after the fourth course of intravenous oxaliplatin (Petit-Laurent et al., 2000). The eruption also improved after 4 days of oral antihistamines and corticosteroids. Despite negative prick tests and intradermal tests after 20 and 30 min, respectively, a delayed erythema and infiltration appeared a day later. Authors proposed the theory of an immunological reaction as a result of a circulating immune complex. In addition, there was a report that T-cell mediated production of cytokines could play an important role (Santini et al., 2001). In their study, serum levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were elevated during the clinical manifestations, while such cytokine levels significantly decreased when the symptoms disappeared. They proposed that oxaliplatin could act as a superantigen, causing lymphocyte over-activation and massive cytokine release; superantigens stimulate T-cell proliferation and cytokine production by direct binding to major histocompatibility complex (MHC) class II molecules on antigen-presenting cells with subsequent stimulation of T cells. These various pathways may be involved in the mechanism of hypersensitivity reactions to oxaliplatin. Further analysis of the mechanism may lead to the development of effective therapeutic strategies without adverse drug reactions.

In this study, there were three cases of anaphylaxis, and all of them had no prior history of allergic reactions. These 64 years old male, 60 years old female, and 52 years old female had colorectal cancer, and received oxaliplatin for adjuvant purpose in one patient and for palliative purpose in two patients. Anaphylaxis developed after ninth to eleventh courses, and all patients who had anaphylaxis to oxaliplatin received their previous chemotherapeutic regimens except oxaliplatin for subsequent courses. There was no case of death due to severe hypersensitivity reaction to oxaliplatin.

We attempted to identify the potential risk factors for hypersensitivity to oxaliplatin. Previous studies that explored risk factors for hypersensitivity reactions to oxaliplatin found younger age, female sex, repeated infusion, higher oxaliplatin dose, and with use of oxaliplatin as salvage therapy to be the predictors for reactions (Kim et al., 2009; Polyzos et al., 2009; Santini et al., 2001; Shao et al., 2010). However, there was no consistently confirmed risk factor. We found that lower dose dexamethasone could be a positive risk factor. Patients who experienced hypersensitivity reactions received significantly less doses of dexamethasone, a mean dose of 11.7 mg, than those who did not experienced hypersensitivity, a mean dose of 14.4 mg ($p<0.001$). Patients who received less than 20mg dose of dexamethasone also had more risk of oxaliplatin hypersensitivity with adjusting age, sex, purpose of chemotherapy and oxaliplatin infusion dose. It has been reported that prophylactic regimens with corticosteroids and antihistamines are successful although effective prophylactic regimen of dexamethasone has not been determined (Bhargava et al., 2004; Brandi et al., 2003; Gowda et al., 2004; Lim et al., 2004; Maindrault-Goebel et al., 2005; Thomas et al., 2003). In a recent study, it has been reported that high dose dexamethasone plus antihistamine prevented colorectal cancer patients treated with modified FOLFOX-6 from hypersensitivity reaction to oxaliplatin (Kidera et al., 2011). In other study, high dose dexamethasone (20mg) and low dose dexamethasone (8mg) were compared to evaluate the prophylactic effect to hypersensitivity reactions (Markman et al., 1999). Dexamethasone of 20 mg has been shown to be safe and effective for the prophylaxis of paclitaxel-associated hypersensitivity reactions. Hypersensitivity developed significantly more cases in the patients who were administered low dose dexamethasone. They reported that these premedication had not increased the incidence of adverse effects related to the high dose of dexamethasone, such as exacerbation of diabetes, osteoporosis, and compression fracture. We did not evaluate the difference of premedications and total oxaliplatin infusion cycles between both groups. All patients received premedication to prevent to emesis, and total infusion cycles were determined by diverse causes including neuropathy, completion of planned cycle, disease progression, and

hypersensitivity. Dexamethasone seems to be a good choice of premedication, but there were also some reports which showed dexamethasone as premedication could not prevent all oxaliplatn-related hypersensitivity reactions (Brandi et al., 2003; Ichikawa et al., 2009; Siu et al., 2006). We need more large studies to evaluate the efficacy and the appropriate dose of dexamethasone for prophylaxis.

Several limitations of this study should be noted. First, most patients who received oxaliplatin received premedication with antihistamine and dexamethasone to prevent mostly emesis, and because of that, the severity of the reaction could have been altered in the group of patients manifesting mild reactions. Second, hypersensitivity reactions after departure from hospital might have been unrecorded because many of patients received chemotherapy at outpatients department, staying at hospital only for several hours. Third, some medical records were insufficient or inadequate, especially the exact onset times in many cases. In addition, we could not confirm the suspected drug by skin test because this study was done retrospectively and most patients were not consultated to allergiests. To resolve these problems, further studies are needed based on a prospective design. However, this is the first systematic report on oxaliplatin hypersensitivity in Korea and it provides the overview of prevalence, clinical manifestations and a possible risk factor in Koreans.

In conclusion, the prevalence of hypersensitivity to oxaliplatin was 10.7%. Most common symptom was cutaneous manifestation. Anaphylaxis occurred in 0.76% of patients. Lower dexamethasone dose could be associated with hypersensitivity reactions.

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