

Short Communication

Allergic Reactions to Oxaliplatin in a Single Institute in Japan

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Allergic reactions to oxaliplatin can be severe and are an important cause of discontinuation of treatment. A retrospective review was performed for 105 patients who received FOLFOX regimens between May 2005 and June 2007. Twenty-five cases (23.8%) of allergic reactions were identified, including 9 late onset reactions (8.6%) and 16 immediate reactions (15.2%). Severe allergy (Grades 3 and 4) occurred in seven patients (6.7%). Re-introduction of FOLFOX was attempted for seven immediate onset patients with a severity grade of 1 or 2, and three of these patients (42.9%) showed relapse of allergy. In ~10% of the patients, FOLFOX had to be discontinued due to allergy before the disease became refractory to the regimen. Our experience indicates that allergy to oxaliplatin may be a significant concern and that methods are required for suppression of this allergy.

Key words: oxaliplatin – FOLFOX – allergy – hypoxemia

INTRODUCTION

Oxaliplatin is a useful drug for colorectal cancer and the FOLFOX regimen including this drug is a standard treatment for advanced colorectal cancer. Oxaliplatin is a member of the family of platinum drugs that also includes cisplatin and carboplatin. Hypersensitivity reactions to platinum-containing compounds are well described and potentially life threatening. These reactions were thought to be less frequent with oxaliplatin compared with cisplatin or carboplatin, but with expanded use of oxaliplatin in various malignancies, an increased number of hypersensitivity reactions have been reported with an incidence of 10–12%, including a rate of >1% for severe reactions (1). In Japan, oxaliplatin has been approved as a treatment for advanced colorectal cancer for 3 years. Here, we examine the clinical features of hypersensitivity reactions with the FOLFOX regimen.

PATIENTS AND METHODS

We reviewed the records of 105 patients who received chemotherapy using premedication with dexamethasone (8 mg/body) and a 5-HT₃ receptor antagonist followed by a FOLFOX4 regimen [oxaliplatin 85 mg/m² day 1, L-leucovorin 100 mg/m² days 1 and 2, 5-fluorouracil (5-FU) 400 mg/m² bolus days 1 and 2, and 600 mg/m² continuous infusion days 1 and 2, every 2 weeks] or a modified FOLFOX6 regimen (oxaliplatin 85 mg/m² day 1, L-leucovorin 200 mg/m² days 1 and 2, 5-FU 400 mg/m² bolus days 1 and 2, and 600 mg/m² continuous infusion days 1 and 2) in the Department of Clinical Oncology, Yokohama City University Hospital, between May 2005 and June 2007.

The treatment regimen, treatment line, symptoms of hypersensitivity and grading (by CTCAE v3.0), and oxaliplatin dose and cumulative dose (mg/m²) were analyzed. Patients showing mild allergic symptoms (Grade 1 or 2) and potential for a good prognosis with continued treatment were given further FOLFOX therapy. This therapy included an increased infusion time of oxaliplatin from 2 to 4 h (2) and was given after preventive treatment with dexchlorpheniramine, H₂-blockade and the same doses of dexamethasone and a 5-HT₃ receptor antagonist as those given before

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development of allergic symptoms. Epinephrine was not utilized as premedication. Recurrence of allergic episodes after re-introduction of FOLFOX was also analyzed.

Allergy to platinum salts is classically defined as a Type I allergy with an immediate hypersensitivity reaction showing itching, urticaria, rash, angioedema, bronchospasm and hypotension. In the study, occurrence of these symptoms was reviewed in immediate reactions (occurring during administration of oxaliplatin) and in late onset allergic skin lesions (occurring 24 h or more after oxaliplatin administration). In cases with an immediate reaction, oxygen saturation (SpO₂) was measured continuously and hypoxemia was diagnosed for patients with SpO₂ < 92% (3). We also retrospectively reviewed the percentage and number of eosinophils in blood drawn before FOLFOX treatment, during the previous cycle of allergy and on the day of the allergic reaction. Eosinophilia was defined as an eosinocyte count >500/μl. Since white blood cells may decrease in the course of chemotherapy, the percentage of eosinophils was also investigated.

RESULTS

Twenty-five cases (23.8%) of allergic reactions were identified in the course of FOLFOX treatment, including 9 late onset reactions (8.6%, Table 1) and 16 immediate reactions (15.2%, Table 2). Six cases (5.7%, Table 2) showed severe allergy (Grade 3 or 4), but there were no deaths due to allergy.

In the late onset cases, all patients were identified by skin lesions showing allergy of Grade 1 or 2. The median onset time was 6 days (range: 3–9 days) after oxaliplatin administration. The skin lesions of eight patients (88.9%) were

localized and only one patient (No. 8) showed erythroderma over the whole body. FOLFOX was discontinued because of tumor progression in one patient (No. 4), but was re-introduced in the other eight patients. Seven of these patients tolerated this therapy with premedication for allergy, whereas patient No. 8 redeveloped whole body erythroderma, despite premedication for allergy. Interestingly, patient No. 5 showed wheal in the superior limbs after exposure to sunlight as a photosensitive reaction which he had not experienced previously.

There were 19 episodes of immediate reactions in 16 patients. Onset of allergy occurred in the course of dripping administration of oxaliplatin in all these patients (Table 2), including five episodes of Grade 3 severity (26.3%) and one of Grade 4 (5.2%) that required discontinuation of FOLFOX. The patient with Grade 4 anaphylactic shock showed hypotension requiring catecholamine administration and hypoxemia that required oxygen administration during a hospital stay of 2 days. There were six episodes of Grade 1 severity (31.6%) and six of Grade 2 (31.6%) in 10 patients, with cessation of FOLFOX due to tumor progression or patient refusal in two cases and re-introduction of FOLFOX for the other seven patients. Three of these seven patients showed relapse of Grade 2 or 3 allergy within three cycles after re-introduction and FOLFOX therapy was discontinued. Various symptoms of immediate onset allergy were observed (Table 2), with hypoxemia detected in 42% of the cases. All cases of Grade 3 or 4 severity showed SpO₂ ≤ 92% and two cases of Grade 2 allergy also showed hypoxemia. However, only two patients complained of dyspnea. Eosinophilia defined as an eosinophil count >500/μl was detected in only one patient on the day of the allergic reaction, and >6% eosinophils was found in four cases on the day of allergy and in one case before treatment.

Table 1. Patients with late onset allergic reactions

No.	Age (years)	Gender	Grade	Skin lesion		Onset course	Onset time (days)	Additional course	Reason for discontinuation
				Type	Region				
1	67	M	1	w	T	7	7	3	Neuropathy
2	68	M	1	er	F	4	3	4	PD
3	73	M	1	ec	LL	3	7	3	Ongoing
4	65	M	1	w	F	15	9	0	PD
5	60	M	1	w	UL	6	7	6	PD
6	61	F	1	ec	T	7	7	5	PD
7	76	M	1	er	F	10	3	2	PD
8	62	F	2	er	W	2	3	1	Allergy
			(2)	er	W	(1)	(3)		
9	70	M	2	er	F	2	3	6	PD
Median	67					6			

PD, progressive disease; w, wheal; er, erythema; ec, eczematoid; T, trunk; F, face; LL, lower limbs; UL, upper limbs; W, whole body.

Table 2. Patients with immediate allergic reactions

No.	Gender	Age (years)	Grade	Skin lesion		Vomiting	Fever/ chill	Hypotension	Dyspnea	Hypoxemia	Onset course	Re-introduction	Additional course	Reason for discontinuation
				Type	Region									
1	M	58	1	er	F, N, Pr	—	—	—	—	—	3	+	5	PD
2	M	72	1	er	W	—	—	—	—	—	6	—	0	PD
3	M		1	w	F	—	—	—	—	—	6	+	0	ongoing
4	F	62	1	er	Pr	—	—	—	—	—	7	—	0	Patient refusal
5	M	70	2	er	W, injection of the conjunctiva	—	—	+	—	SpO ₂ = 92%	8	+	5	PD
6	F	59	2	w	T	—	—	—	—	91%	5	—	0	Allergy
7	M	66	2	er	F, N, Pr	—	—	—	—	—	5	—	0	PD
8	M	65	2	w	T	—	—	—	—	—	12	—	0	PD
9	F	73	2	w, er	F, W	—	—	—	—	—	7	+	4	Ongoing
10	M	64	3	u	W	+	+	—	+	86%	12	—	0	Allergy
11	M	52	3	er	F, N, Pa	+	—	—	—	90%	8	—	0	Allergy
12	M	62	3	er	W	—	+	—	—	92%	9	—	0	Allergy
13	M	64	4	er	W	+	+	+	+	81%	8	—	0	Allergy
14	M	64	1	w	F	—	—	—	—	—	6	+	2	Relapse
			(3)	(w)	(N, Pa, UL)	(+)	(—)	(—)	(—)	(90%)	(+2)	(—)		
15	F	55	1	w	F	—	—	—	—	—	10	+	3	Relapse
			(3)	(u)	(W)	(—)	(+)	(—)	(+)	(90%)	(+3)	(—)		
16	M	72	2	er	W	—	—	—	—	—	3	+	2	Relapse
			(2)	(er)	(W, injection of the conjunctiva	(—)	(—)	(—)	(—)	(—)	(+2)	(—)		
Median	64										7			

u, urticaria; N, neck; Pr, precordial region; Pa, palm.

DISCUSSION

The mechanism of platinum allergy is unclear. The first report of a hypersensitive reaction to platinum was a case showing asthmatic fit, urticaria and platinum-specific IgE after inhalation of platinum (4). Platinum-based anti-cancer drugs have been used extensively for many types of cancers and reports of hypersensitive reactions have increased (5,6,7), with most of these occurring after multiple cycles of therapy. Carboplatin induces hypersensitive reactions most frequently with a reported incidence of 12–30% (5), whereas cisplatin allergy occurs at a rate of 5–20% (7). For oxaliplatin, incidences of 8–19% have been reported for all reactions and 1–7.3% for severe reactions (6). In our institute, the incidence of immediate onset allergy was 15.2% and that of severe reactions was 6.7%, with FOLFOX therapy discontinued in 8.6% of the patients due to allergy before the disease became refractory to the treatment.

Adverse events and infusional reactions are distinguished in the DRUGDEX hypersensitivity index (8). Infusional or idiosyncratic reactions are defined as abnormal reactions to a drug without an antibody effect, in which onset might not be immediate and the symptoms are chills, fever, abdominal pain, nausea and diarrhea with or without hypotension (9). Maindrault-Goebel et al. have proposed a definition of Type II allergy resulting in hemolytic anemia or thrombopenia, and Type III allergy resulting in chronic urticaria, joint pain and proteinuria for hypersensitive reactions to oxaliplatin. In our institution, we did not experience infusional reactions or Type II allergies with oxaliplatin. The 16 cases of immediate onset allergy all occurred in the course of dripping administration of oxaliplatin, indicating that they were Type I allergic reactions. Nine cases showed late onset allergy, but we cannot be certain that these were induced by oxaliplatin alone. It is also possible that the allergies might have been due to 5-FU or other causes. However, the nine cases of late onset allergy after the FOLFOX regimen might be the examples of Type III allergy if they were induced by oxaliplatin. The late onset cases were all identified by temporary skin lesions and the reactions were well controlled by premedication.

In the immediate onset cases, the patients showed various symptoms. In previous reports, ~40% of allergic patients showed rash or cutaneous reactions (6,10), but in our study, all patients had cutaneous lesions to a greater or lesser extent. Therefore, careful and frequent inspection for skin lesions in dripping administration of oxaliplatin is useful for early detection of an immediate reaction. Hypotension and dyspnea are severe allergic complaints, and among our cases, one patient with a reaction of Grade 4 severity required administration of oxygen for hypoxemia and dyspnea and continuous infusion of catecholamines, and five patients with Grade 3 severity required oxygen. Siu et al. (10) found rates of 14.8% for dyspnea and 7.4% for hypotension in patients with hypersensitivity to

oxaliplatin, and Maindrault-Goebel et al. (6) reported rates of 47.6% for respiratory symptoms and 7.1% for anaphylactic shock (hypotension) among 42 allergic patients. Our results showed a rate of hypotension of 10.5%. Only 15.8% of the patients had dyspnea, but 42% of the immediate onset cases showed hypoxemia and 36.8% of the patients required oxygen administration. Wheeze on auscultation was only detected in one case. These results suggest that respiratory problems due to oxaliplatin allergy may be more severe than initially apparent, and a saturation monitor should always be used in cases of immediate onset allergy.

Re-introduction of therapy was tried for seven patients and three (42.9%) showed relapse of allergy, of whom two showed a severe (Grade 3) allergy. Siu et al. reported four cases (28.6%) of relapse and two (14.3%) of severe relapse in 14 patients who were re-exposed to oxaliplatin with premedication, out of a total of 27 patients with an allergic reaction. Maindrault-Goebel et al. found that 7 of 9 patients showed relapse of allergy following re-introduction of therapy without modification, and that 7 of 15 patients had relapse following re-introduction of therapy with an increased duration of infusion, including 2 with anaphylactic shock. Therefore, re-introduction of therapy requires premedication with steroids and histamine receptor antagonists, and patients should be monitored closely for relapse of allergy.

We obtained the eosinophil number and ratio before introduction of FOLFOX, during the previous cycle of allergy and on the day of the allergic reaction, but an allergic response could not be predicted using these data. As an example, Leguy-Seguin et al. (4) have suggested that skin testing of platinum drugs gives good negative predictive values for allergic responses. However, further studies are needed to establish a good predictive method for oxaliplatin allergy. Consequently, FOLFOX had to be discontinued in ~10% of the patients because of allergy before the disease became refractory to the regimen. Overall, our results suggest that oxaliplatin allergy is an important concern and that methods for suppression of the allergic response are required.

Conflict of interest statement

None declared.

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Appendix

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