

ORIGINAL ARTICLE

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Oxaliplatin-induced allergic reaction in patients with colorectal cancer in Japan

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Abstract

Background. Oxaliplatin is a platinum compound that is clinically effective for colorectal cancer (CRC), in combination with 5-fluorouracil (5-FU) and leucovorin (LV), and it is widely used for metastatic disease and for the adjuvant treatment of stage III CRC. With the increasing use of oxaliplatin in Japan, serious adverse events have been experienced other than hematologic and neurologic toxicities.

Methods. In order to clarify the clinical features of allergic reactions to oxaliplatin, we retrospectively investigated CRC patients who had received oxaliplatin-based chemotherapies.

Results. One hundred and twenty-five CRC patients who had been treated with FOLFOX regimens (containing oxaliplatin, 5-FU, and LV) were examined, and 21 patients (17%) were found to have developed allergic reactions. Sixteen patients (13%) had grade 1/2 adverse events, classified according to the common terminology criteria for adverse events (CTC-AE) version 3.0 and 5 (4%) had grade 3/4 adverse events. The allergic reaction appeared after a median number of nine cycles (range, 2–15 cycles). Previous chemotherapy included 5-FU/LV, CPT-11, and S-1. All of the patients with allergic reactions recovered completely when treated with antiallergy drugs. Oxaliplatin was reintroduced in 11 patients, with the use of prophylactic agents; allergic reaction to the reintroduction was not observed in

8 patients and grade 1/2 allergic reactions developed in 3 patients. No correlation was identified between allergic reaction and patients' background characteristics such as sex, history of allergy, and profile of other adverse events.

Conclusion. Allergic reactions to oxaliplatin remain an important issue for patients being able to safely continue effective chemotherapies; further analysis will be needed to establish methods for the prediction and prophylaxis of such reactions.

Key words Colorectal cancer · Oxaliplatin · Allergic reaction

Introduction

Oxaliplatin, a third-generation platinum anticancer drug, is effective for the treatment of metastatic colorectal cancer (CRC). Currently, FOLFOX, consisting of oxaliplatin, 5-fluorouracil (5-FU), and leucovorin (LV), has become the standard regimen for metastatic colorectal cancer.¹ Superior overall survival with FOLFOX4 (see below for specific agents and doses) over IFL and IROX regimens has been reported in a phase III clinical trial.² Recent randomized phase III trials employing FOLFOX plus the molecular target drug bevacizumab have exhibited further improvement of therapeutic effects in CRC patients.³ A recent European adjuvant trial in colon cancer (MOSAIC) demonstrated significant improvement in 3-year disease-free survival when oxaliplatin was added to infusional 5-FU and leucovorin.⁴

Cumulative sensory neurotoxicity and neutropenia are well-known dose-limiting factors of oxaliplatin. With the increasing use of the treatment, allergic reactions to oxaliplatin have frequently become apparent. Recent studies have reported that oxaliplatin-induced allergic reactions occurred at a frequency of 3.6%–18.9%, and at more than six cycles of therapy, although patients rarely suffered severe allergic reactions.^{4–9} Other platinum compounds, cis-

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platin and carboplatin, have also been reported as causes of allergic reactions.¹⁰

Oxaliplatin-induced allergic reaction is an important adverse effect, which determines whether or not the therapy is able to be continued. There are several reports of allergic reactions to oxaliplatin in Western countries. However, only limited information has been available in Japanese patients because of the short period of usage experienced since government approval was granted. In order to clarify the clinical features of allergic reactions to oxaliplatin in Japan, we retrospectively investigated CRC patients who had received oxaliplatin-based therapies. We determined the number of treatment cycles before the allergic reactions appeared, evaluated the treatments for the allergic reactions and the safety of reintroduction of oxaliplatin, and we analyzed the background of the allergic patients in order to identify factors that induced the allergic reactions.

Patients and methods

Patients who were given oxaliplatin-containing regimens, i.e., FOLFOX4 (oxaliplatin 85 mg/m² day 1, LV 100 mg/m² days 1 and 2, and continuous 5-FU 600 mg/m² days 1 and 2, bolus 5-FU 400 mg/m² days 1 and 2), FOLFOX6 (oxaliplatin 100 mg/m² day 1, LV 200 mg/m² day 1, and continuous 5-FU 1200–1500 mg/m² days 1 and 2, bolus 5-FU 400 mg/m² day 1), and modified FOLFOX6 (oxaliplatin 85 mg/m² day 1, LV 200 mg/m² day 1, and continuous 5-FU 1200–1500 mg/m² days 1 and 2, bolus 5-FU 400 mg/m² day 1) for the treatment of advanced and recurrent CRC by the Kyushu Medical Oncology Group (KMOG), between April 2005 and November 2006, were analyzed. Adverse events were graded according to the common terminology criteria for adverse events (CTCAE), version 3.0.

We examined patients' age, sex, primary and metastatic lesions, prior chemotherapies, performance status, treatment regimens, total number of treatment courses, the time of occurrence of allergy, allergic symptoms, allergy grade, treatment for the allergy, outcome of treatment for the allergy, reintroduction of oxaliplatin, prophylactic agents, and post-treatment characteristics.

Using Fisher's exact test, the relationship between allergic reaction to oxaliplatin and several background factors including sex, hematologic toxicity, neurologic toxicity, and history of allergy were statistically analyzed.

Results

We identified 125 CRC patients who received oxaliplatin-containing regimens between April 2005 and November 2006. The median number of courses of the regimens was eight (range, 1–17). None of the patients had previously received platinum-containing regimens. Twenty-one patients (17.0%; see Table 1 for characteristics) experienced allergic reactions of various grades to oxaliplatin-containing regimens, and 5 (4.0%) of these allergic patients

Table 1. Patient characteristics

Characteristics	Number (%)
Number of patients	21
Median age (years; range)	60 (42–78)
Sex; male/female	11:10
Cancer origin	
Cecum	2
Ascending	6
Transverse	1
Descending	0
Sigmoid	5
Rectum	7
Extent of disease	
Liver	10
Lung	9
Peritoneum	9
Pleura	1
Bone	1
Other	5
Local	2
PS	
0	14
1	6
2	1
Prior chemotherapy	
5-FU/LV	14 (66.7)
CPT-11	13 (61.9)
Oral fluoropyrimidines	11 (52.4)
MMC	1 (4.7)
None	3 (14.3)

PS, performance status; 5-FU/LV, 5-fluorouracil/leucovorin; CPT-11, MMC, mitomycin C

developed severe reactions of CTCAE grade 3 (Table 2). The median age of the allergic patients was 60 years (range, 42–78 years) and the number of male and female patients was 11 and 10, respectively (Table 1). The numbers of patients with Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, and 2 were 14, 6, and 1, respectively. Cancer origin and the extent of the disease are listed in Table 1. Prior chemotherapies given as the first-line or in the adjuvant setting included 5-FU/LV (66.7%), CPT-11 (61.9%), and oral fluoropyrimidines (52.4%). In the 104 CRC patients without allergic reactions to the FOLFOX regimens, the median age was 61 years (range, 29–84 years) and the number of male and female patients was 62 and 42, respectively. The median number of therapeutic courses was eight (range, 1–17). Forty-four percent of these patients experienced CTCAE grade 3/4 hematologic toxicity and 58% had CTCAE grade 3/4 neurotoxicity.

Most of the allergic patients had been treated with the modified FOLFOX6 regimen (85.7%) but three had been treated with the FOLFOX4 regimen and one with the FOLFOX6 regimen (Table 2). Allergic reactions to oxaliplatin were observed after a median of nine cycles (range, 2–15 cycles). Most of the patients completely recovered from the allergic reactions with the use of antihistamine and glycyrrhizin. However, patients who developed a grade 3 reaction additionally required steroid, epinephrine, and oxygen administration. These patients were treated according to the standard methods for treating allergic diseases. Although FOLFOX was discontinued in 11 patients (52.4%), who were given other anticancer agents, oxalipla-

tin was reintroduced in 10 patients (47.6%) who had developed grade 1 and 2 reactions. Before reintroducing oxaliplatin, we precisely explained to the patients the risks and benefits of continuing the therapy and the therapeutic methods for preventing possible allergic reactions, and we subsequently acquired their informed consent. Six patients with grade 1 and 2 allergic reactions did not continue with the oxaliplatin-based therapy, either because of the patients' refusal or because of the doctor's decision, based on the current therapy showing insufficient clinical benefits. We did not reintroduce oxaliplatin to the patients with grade 3 allergic reactions. When reintroducing oxaliplatin, prophylactic doses of dexamethasone were increased in nine

patients, H1 and H2 blockers were added in eight patients, the dose of oxaliplatin was reduced in one patient and the duration of oxaliplatin infusion was prolonged in one patient. Two patients with grade 1 allergic reactions continued with the same FOLFOX regimens without any changes in prophylaxis. One of these two patients continued with three more courses without any symptoms and the other experienced only a grade 1 reaction. Two patients with grade 2 allergic reactions again had grade 2 reactions on the reintroduction of oxaliplatin, despite an increase in the dexamethasone dose and the addition of antihistamines, and oxaliplatin was subsequently discontinued. Of the 21 patients with allergic reactions to FOLFOX, 38% experienced CTCAE grade 3 or 4 hematologic toxicity and 67% patients suffered neurotoxicity (Table 3). In the 125 patients overall (i.e., both the group with and the group without allergic reactions), only 1 patient developed grade 3 neurotoxicity.

In order to identify the factors predictive of the occurrence of oxaliplatin-induced allergic reaction in Japanese patients, we compared six patient background factors (sex, age, number of oxaliplatin-containing chemotherapy courses, hematologic toxicity, neurologic toxicity, and history of allergy) between the 21 CRC patients with allergic reactions and the 104 patients without allergic reactions. No correlations were observed between the occurrence of allergy and these six factors ($P = 0.63$, not evaluable [NE], NE, $P = 0.64$, $P = 0.48$, and $P = 1.00$, respectively). Even in the limited patient population that received more than six courses of FOLFOX ($n = 65$), there were no correlations between allergy and the background factors of sex, hematologic toxicity, neurologic toxicity, and history of allergy ($P = 0.80$, $P = 0.32$, $P = 1.00$, and $P = 1.00$, respectively; Table 3).

Table 2. Allergic reactions

	Number (%)
Grade of allergy	
1	7 (33.3)
2	9 (42.9)
3	5 (23.8)
4	0 (0)
Chemotherapy regimen	
FOLFOX4	3 (14.3)
FOLFOX6	1 (4.8)
Modified FOLFOX6	18 (85.7)
Median number of chemotherapy courses (range)	9 (2–15)
Following treatments	
FOLFOX reintroduction	10 (47.6)
FOLFIRI	3 (14.3)
5-FU/LV	6 (28.6)
Oral fluorouracil	1 (4.8)
BSC	1 (4.8)
Prophylaxis for reintroduction	
Increased dexamethasone	9 (42.9)
Antihistamines	8 (38.1)
Decreased OHP	1 (4.8)
Extension of time	1 (4.8)
None	2 (9.5)
Allergic reaction after reintroduction	
Grade 0	8 (38.1)
Grade 1	1 (4.8)
Grade 2	2 (9.5)
Grade 3	0 (0)
Grade 4	0 (0)

BSC, best supportive care; OHP, oxaliplatin

Discussion

An oxaliplatin-containing regimen, FOLFOX, is the current standard therapy for advanced and recurrent CRC. The response rate of FOLFOX in the first-line setting for

Table 3. Clinical features of patients with and without allergic reactions

	Nonallergic	Allergic	<i>P</i> value
All patients			
Sex (M/F)	62/42	11/10	0.63
Age (years; range)	61 (29–84)	62 (42–78)	NE
Number of courses (range)	8 (1–17)	9 (2–15)	NE
Hematologic toxicity (grade 3/4)	46 (44.2%)	8 (38.1%)	0.64
Neurologic toxicity			
(Grade 1/2/3)	24/35/1	5/8/1	NE
(All grades)	60 (57.7%)	14 (66.7%)	0.48
History of allergy	16 (15.4%)	3 (14.3%)	1
Patients with more than six courses			
Sex (M/F)	38/27	11/9	0.8
Hematologic toxicity (grade 3/4)	35 (53.8%)	8 (40.0%)	0.32
Neurologic toxicity (all grades)	42 (64.6%)	13 (65.0%)	1
History of allergy	9 (13.8%)	3 (15.0%)	1

NE, not evaluable

advanced disease was 50.7% and the median survival time was 16.2 months.² FOLFOX has also been used as an adjuvant chemotherapy for CRC.⁴ Dose-limiting toxicities were cumulative sensory neurotoxicity and neutropenia.² With the increasing use of oxaliplatin in clinical practice, oxaliplatin-induced allergic reactions have been encountered frequently. Recent reports showed that the incidence of the allergic reactions induced by oxaliplatin ranged from 3.6% to 18.9%.⁴⁻⁹ In a randomized phase III trial (MOSAIC trial), 10.3% of the 1108 patients experienced allergic reactions, and 2.3% and 0.6% of the patients, respectively, had grade 3 and grade 4 allergic reactions.⁴ Similar to these observations, we found that 17% of Japanese CRC patients who were treated with oxaliplatin-containing regimens experienced allergic reactions, with 5% of them exhibiting grade 3/4 allergy. The reaction has been reported to occur after multiple therapeutic courses (median, 4–7 courses).⁴⁻⁹ Similarly, our data showed that allergy occurred after a median nine courses of chemotherapy. We found no significant relationships between the occurrence of allergic reactions and the number of treatment regimens, as was also shown in previous reports.⁷

It has been reported that all platinum compounds induce allergic reactions.¹¹⁻¹⁴ However, the exact mechanism of the allergy remains unclear. The pathophysiology of oxaliplatin-induced allergic reactions is also undetermined, although mechanisms similar to those shown for other platinum compounds are thought to be involved. The classical understanding was that platinum induced a type I allergic reaction mediated by immunoglobulin E, followed by histamine release.^{15,16} Recent studies have suggested novel mechanisms of the reaction. Increases in the T-cell-mediated production of cytokines, such as tumor necrosis factor (TNF)- α and interleukin (IL)-6, were reported to be induced by a superantigen-like function of platinum in mononuclear cells.¹⁷ On the other hand, altered antigen-presentation by platinum-bound peptide was also shown in the context of HLA molecules.¹⁸ Further analysis of the mechanism of platinum-induced allergy may lead to the development of effective therapeutic strategies for CRC and other malignant diseases.

While factors predictive of allergic reaction to platinum are still not clarified, previous studies have suggested that increasing numbers of chemotherapy courses with carboplatin may enhance susceptibility to allergic reactions.^{19,20} The frequency of allergic reactions to carboplatin was reported to be 0.92% in the fifth course, 6.5% in the sixth course, and 19.5% in the eighth course.²⁰ Markmen et al.¹⁹ reported that 27% of the patients who had received more than seven courses of carboplatin had allergic reactions. In patients receiving oxaliplatin, many studies demonstrated that the allergic reaction often appeared after six cycles of chemotherapy,⁴⁻⁹ and our observation demonstrated that it occurred after more than eight cycles. Other factors predictive of an allergic reaction to oxaliplatin were not clarified in an investigation of 42 patients.⁷ Lee et al.²¹ analyzed the possible association of oxaliplatin-induced severe anaphylactic reactions with the type and number of metastatic sites. No significant association was found between the

occurrence of oxaliplatin-induced severe anaphylactic reactions and these factors. Although we examined the correlation between allergic reaction to oxaliplatin and various potential predictive factors such as sex, hematologic toxicity, neurotoxicity, and history of allergy, no correlations were identified with these factors, probably because the number of patients with allergic reactions was not adequate for obtaining statistical significance. A large-scale clinical study might reveal the risk factors for allergic reaction.

Various studies have reported that the allergic reactions to oxaliplatin were immediately alleviated with antihistamines and steroids. Severe anaphylactic reactions were often alleviated by high-dose steroids and no mortality has been reported.⁴⁻⁹ However, the reintroduction of oxaliplatin after the development of an allergic reaction has been an important issue. Several groups have safely carried out the reintroduction of oxaliplatin with the use of prophylactic agents such as antihistamines and steroids, dose reduction of oxaliplatin, extension of administration time, and desensitization therapy according to a carboplatin protocol.^{8,22} On the other hand, Maindrault-Goebel et al.⁷ reported that 58% of patients who experienced allergic reactions to oxaliplatin exhibited the reactions again after the reintroduction of oxaliplatin even with dose reduction and extension of administration time. Brandi et al.⁹ reported that 83% (five of six patients) of patients developed allergic reactions with the reintroduction of oxaliplatin with prophylactic dexamethasone and antihistamines. Sui et al.⁶ reintroduced oxaliplatin in 14 patients who had developed grade 1/2 allergic reaction by using prophylactic dexamethasone and antihistamine. Four of these 14 patients (28.6%) had allergic reactions again, and 2 of them (14.6%) developed grade 3/4 severe reaction.⁶ In our study, we safely reintroduced oxaliplatin in 8 patients with modification of prophylactic agents. Although various methods have been used for reintroduction, such as premedication, dose reduction of oxaliplatin, extension of administration time, and desensitization, no standardized protocol for reintroduction was available during the period of the present study, and allergic reactions still occurred even with the prophylactic measures we used. To prevent life-threatening anaphylactic reaction being induced by the reintroduction of oxaliplatin, the development of standard methods for reintroduction is urgently needed.

Recent investigations have demonstrated a prominent survival benefit conferred in CRC patients by oxaliplatin-containing regimens such as FOLFOX, with appropriate molecular target drugs. Alternative strategies of oxaliplatin-based therapy with decreased cumulative neurologic toxicity, such as the OPTIMOX regimen, have also been examined.²³ It is important to further clarify the pathophysiology of allergic reactions to oxaliplatin in order to establish a safe method for continuing this chemotherapy.

Conflict of interest statement

T.Esaki received a research funding from Astrazeneca, Nippon Kayaku, Taiho Pharmaceutical. K. Mitsugi

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