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Clinical features of hypersensitivity reactions to oxaliplatin among Chinese patients with colorectal cancer

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[Abstract] Background and Objective: Oxaliplatin is one of the effective drugs for the treatment of advanced colorectal cancer (CRC). Oxaliplatin-induced allergic reactions in European and American patients have been reported, but in China there are only a few case reports. This study investigated the incidence rate and characteristics of oxaliplatin-induced allergic reactions in Chinese patients with CRC. **Methods:** Clinical data of 109 patients with advanced CRC receiving oxaliplatin plus capecitabine (the XELOX regimen) as first-line therapy were collected and analyzed retrospectively. **Results:** Among the 109 patients, 13 (11.9%) patients had hypersensitivity. In 546 cycles, 23 (4.2%) cycles involved hypersensitivity. Grade-I, -II, and -III reactions were seen in 13 cycles, 8 cycles, and 2 cycles, respectively, and no grade-IV reaction was observed. Allergic reactions usually occurred at the median time during the fifth cycle (range, the 1st–8th cycle) of oxaliplatin-containing therapy, and the cumulative oxaliplatin dose was 1200 mg (range, 400–1600 mg). Symptoms associated with anaphylaxis appeared 5–360 min (median, 180 min) after oxaliplatin infusion, and were relieved after withdrawing the oxaliplatin infusion and treating with antiallergic drugs. A total of 8 patients continued to receive oxaliplatin therapy after prophylactic administration of antiallergic drugs, such as steroids, and 4 patients did not report persistent allergic reactions. Compared with men, oxaliplatin-induced allergic reactions were more commonly seen in women patients ($P < 0.05$), while age, body surface area, performance status, tumor location, and pathologic type showed no significant difference. **Conclusion:** Oxaliplatin-induced allergic reactions occurred in Chinese patients with CRC, and the incidence rate, occurrence time, degree of severity, and clinical outcome were consistent with literature published abroad.

Key words: Oxaliplatin, anaphylaxis, colorectal neoplasm

Oxaliplatin is a third-generation platinum antineoplastic agent. The 2-amino-cyclohexane-platinum DNA that oxaliplatin forms is more hydrophobic than that formed by cisplatin and carboplatin.¹ The renal toxicity of oxaliplatin is milder than cisplatin, while its bone marrow suppression action is weaker than carboplatin. Nervous system toxicity is the main dose-limiting side effect for oxaliplatin.¹ Oxaliplatin is now widely used as a palliative chemotherapy for patients with advanced colorectal cancers (CRC) and as postoperative adjuvant chemotherapy for early CRC. In recent years, hypersensitivity reactions to oxaliplatin

have caught much attention. However, the rate of hypersensitivity reactions is not consistent between published reports,^{2,3} that is, in reports published overseas, the rate of hypersensitivity reactions to oxaliplatin was 0.55%–15%, whereas only occasional cases were reported in China. Therefore, we collected case information on 109 patients with recurrent and metastatic CRC who were receiving oxaliplatin + capecitabine (the XELOX regimen) as first-line palliative chemotherapy, and analyzed the incidence, the time of occurrence, and severity of hypersensitivity reactions to oxaliplatin, as well as clinical outcomes of these patients, providing a basis for the prevention and treatment of hypersensitivity reactions caused by oxaliplatin in patients with CRC in China.

Materials and Methods

General Information

A total of 109 patients with metastatic or advanced CRC, or

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both [according to the American Joint Committee on Cancer (AJCC) TNM 2002 staging method] who underwent treatment at the Sun Yat-sen Cancer Center from November 2003 to June 2008 were recruited. Diagnosis was confirmed by histopathology. A total of 59 patients were men and 50 were women, with a median age of 53 years (range, 12–79 years). There were 52 patients with rectal cancer, 57 with colon cancer; 93 with adenocarcinoma, 16 with mucinous adenocarcinoma; 30 with liver metastasis, 14 with lung metastasis, 4 with bone metastases, 20 with metastasis in the abdominal or pelvic cavity; 41 with multiple metastatic sites (Table 1).

Table 1 Clinical characteristics of 109 patients with colorectal cancer treated with the XELOX regimen

Characteristic	No hypersensitivity [patient No.(%)]	Hypersensitivity [patient No.(%)]	<i>P</i>
Gender			0.036
Male	56(94.9)	3 (5.1)	
Female	40(80.0)	10(20.0)	
Age (years, median)	53	46	0.110
BSA (m ² , median)	1.6	1.6	0.490
KPS (median)	90	90	0.675
History of hypersensitivity			0.184
No	84(90.3)	9 (9.7)	
Yes	12(75.0)	4(25.0)	
Tumor site			0.610
Colon	51(89.5)	6(10.5)	
Rectal	45(86.5)	7(13.5)	
Pathologic type			0.633
Adenocarcinoma	83(89.3)	10(10.7)	
Mucinous adenocarcinoma	13(81.3)	3(18.7)	
Production of oxaliplatin			0.587
Abroad	44(86.3)	7(13.7)	
At home	52(89.7)	6(10.3)	

Treatment

All patients received the XELOX regimen as their first-line palliative chemotherapy (oxaliplatin 130 mg/m², intravenous infusion for 3 h on day 1; capecitabine 1000 mg/m², oral administration on the first 1–14 days, repeated every 3 weeks). The median total dose of oxaliplatin at the end of the entire program was 1050 mg (range, 120–1680 mg), of which 58 patients used oxaliplatin by injection produced by Jiangsu Hengrui Medicine Co., Ltd., while 51 patients used the product from Sanofi-Aventis Co. No antiallergic treatments were administered at the time of the first treatment with oxaliplatin. A total of 20 patients previously received the FOLFOX regimen as first-line adjuvant chemotherapy and did not show hypersensitivity reactions to oxaliplatin during the earlier treatment.

Evaluation criteria for hypersensitivity reactions

Hypersensitivity reactions were classified according to the Ring-Messmer severity scale for hypersensitivity reactions:⁴ grade I, skin symptoms and/or mild fever reaction; grade II,

measurable, but not life-threatening cardiovascular reactions (tachycardia and hypotension), gastrointestinal disturbances (nausea), and respiratory disturbance; grade III, anaphylactic shock and life-threatening spasms of smooth muscles; and grade IV, cardiac and/or respiratory arrest.

Statistical analysis

Software SPSS16.0 was used for statistical description and analysis. Clinical features of the two patient groups with or without hypersensitivity reactions were compared by χ^2 test or *t* test. *P* < 0.05 was set as the criteria for statistical significance.

Results

Incidence of hypersensitivity reactions, clinical manifestations, and outcomes

Among the 109 patients, hypersensitivity reactions occurred in 13 patients, with an incidence of 11.9%. A total of 546 courses of chemotherapy were administered and hypersensitivity reactions occurred in 23 courses (times), an incidence rate of 4.2%. All hypersensitivity reactions occurred within 360 min of oxaliplatin infusion, with a median time of 180 min (range, 5–360 min). In this study, among the 23 occurrences of hypersensitivity reactions caused by oxaliplatin, 13 (56.5%) were grade I, 8 (34.8%) were grade II, and 2 (8.7%) were grade III, with no grade-IV reactions. After drug withdrawal, symptomatic treatments (such as oxygen inhalation, lowering blood pressure and temperature, etc.) and antiallergic treatments (H1-receptor antagonist and glucocorticoid), all above hypersensitivity reactions remitted, with no related death events. The remission time of the allergic responses was 5–4800 min, with a median time of 90 min. Among the 13 patients with hypersensitivity reactions, 8 received a prophylactic dose of glucocorticoid (an intravenous infusion of dexamethasone 5–10 mg in 100 mL of normal saline) and an H1-receptor antagonist before future infusions of oxaliplatin. Of these patients, 4 did not show hypersensitivity reactions to oxaliplatin again, while the other 4 still showed similar hypersensitivity reactions during later oxaliplatin treatments.

The time of occurrence of hypersensitivity reactions

Of the patients with hypersensitivity reactions, 4 previously received postoperative adjuvant chemotherapy containing the FOLFOX6 regimen. Calculating from the beginning of oxaliplatin access, the median time of occurrence of hypersensitivity reactions was the 5th course of oxaliplatin chemotherapy (range, the 1st–8th course). The total amount of oxaliplatin received by these patients at the time of the hypersensitivity reaction (that is, the median cumulative dose) was 1200 mg (range, 400–1600 mg).

Correlation between hypersensitivity reactions and clinical characteristics

No statistical differences on the incidence of hypersensitivity reactions were detected between the imported and the domestic oxaliplatin (*P* > 0.05). The rate of hypersensitivity reactions to oxaliplatin was higher in women than in men (*P* < 0.05). In patients that showed hypersensitivity reactions and those that had no hypersensitivity reaction, there were no significant differences in

age, body surface area, physical status [Karnofsky Performance Status (KPS) score], tumor location, pathologic type, and so on ($P > 0.05$).

Discussion

Hypersensitivity reactions to oxaliplatin were initially thought to be relatively rare, since a report by Thomas *et al.*² showed that the incidence of oxaliplatin hypersensitivity was only 0.55% (hypersensitivity reactions occurred in only 11 out of 1278 patients). However, in a later report by Brandi *et al.*,¹ the incidence of oxaliplatin hypersensitivity reactions was 13.7% (17 cases of hypersensitivity out of 124 cases) while Siu *et al.*³ reported that in 180 Asian patients receiving oxaliplatin, 27 had hypersensitivity reactions (15%). In addition, a multicenter international study on oxaliplatin/5-FU plus LV as adjuvant treatment of colon cancer calculated the incidence of oxaliplatin hypersensitivity as 10.6%. The clinical data of this study showed that the incidence of oxaliplatin hypersensitivity in Chinese patients was 11.9% (13 cases of hypersensitivity out of 109 patients), consistent with the above 3 reports, suggesting that there was no significant difference in hypersensitivity reactions to oxaliplatin among Chinese patients, Western patients, and patients with other Asian ethnic origins. The reason for the low hypersensitivity rate to oxaliplatin in earlier reports might be fewer courses of chemotherapy using oxaliplatin-containing regimens, when hypersensitivity reactions had not yet occurred. Thus, we did not believe that oxaliplatin rarely caused hypersensitivity reactions according to earlier data. Instead, close observation should become a common practice when using oxaliplatin clinically to diagnose and treat hypersensitivity reactions in a timely fashion.

Our data showed that the median course of the first allergic reaction was the 5th course of oxaliplatin chemotherapy (range, the 1st–8th course), and the cumulative oxaliplatin dose at the time of the hypersensitivity reaction was 400–1600 mg (a median dose of 1200 mg). This was consistent with reports published overseas, in which the median course for oxaliplatin hypersensitivity reactions was the 4th course² to the 9th course,⁵ and the median cumulative dose was 650 mg/m² (100–2400 mg/m²).⁶ The reason for this variation in the median course of oxaliplatin hypersensitivity reactions between our data and the literature might be that we used a 2-week program of oxaliplatin while other authors used a 3-week program, or that it is related to different statuses of previous adjuvant chemotherapy containing oxaliplatin in the patients.

The manifestations and severity of oxaliplatin hypersensitivity reactions vary. While mild cases only show simple skin reactions, severe cases may include anaphylactic shock or even cardiorespiratory arrest.⁵ Based on the number of courses, the 23 occurrences of hypersensitivity in our data comprised 13 grade-I reactions, 8 grade-II reactions, and 2 grade-III reactions, but no grade-IV reactions nor occurrences of anaphylactic shock. Based on case number, out of the 109 patients in our study, 2 patients showed grade-III and-IV reactions, an incidence of 1.8%, similar to the grade III and IV reaction rate of 2.9% reported by Polyzos

*et al.*⁵ and in the MOSAIC study. This indicates that the most common reactions to oxaliplatin are grades I and II, which could completely remit after symptomatic and antiallergic treatment (5-hydroxytryptamine receptor I inhibitors and glucocorticoid). However, we cannot ignore the possibility that grades III and IV reactions may occur.

In hypersensitivity reactions caused by other drugs, hypotension and tachycardia are the most common cardiovascular manifestations, while hypertension rarely occurs. However, Lee *et al.*⁷ reported 2 cases of malignant hypertension, bronchial spasm, and consciousness changes in patients after oxaliplatin infusion and Larzillere *et al.*⁸ found 1 case of hypertensive crisis after oxaliplatin infusion. Our data showed that 2 patients reported hypertension after oxaliplatin infusion, 1 patient showed dyspnea and increased blood pressure to 156/83 mmHg, and 1 patient had increased blood pressure to 200/120 mmHg with chest distress. Recent studies have shown that 5-hydroxytryptamine (serotonin) played a role in the development of hypersensitivity reactions,^{9,10} while type-I and type-II 5-hydroxytryptamine receptors were correlated with systemic hypertension.^{11,12} Therefore, Lee *et al.*⁷ hypothesized that hypertension caused by oxaliplatin might be related to an increase in the blood level of 5-hydroxytryptamine, which needs to be confirmed by further studies. Thus, an increase in blood pressure could also be a manifestation of oxaliplatin hypersensitivity, so blood pressure needs to be monitored during venous infusion to adapt treatment in a timely fashion.

Our data showed that the prophylactic use of antiallergic medications, such as 5-hydroxytryptamine receptor I inhibitors and glucocorticoid, in 8 patients could prevent later oxaliplatin allergy in some patients (efficacy of 50%), while some studies showed that in some patients extending the infusion time of oxaliplatin could reduce the incidence and severity of allergic reactions at later stages.^{13,14} Therefore, for patients with known allergies to oxaliplatin, measures such as antiallergic medications and slower rates of infusion should be adopted to maximize the oxaliplatin tolerance of these patients and to avoid the withdrawal of effective oxaliplatin-containing chemotherapy regimens. However, prophylactic antiallergic measures are not completely effective, so patients with prior life-threatening reactions should avoid using oxaliplatin-containing chemotherapies and change their chemotherapeutic regimen to a better choice.

Our data showed that women had a higher incidence of hypersensitivity to oxaliplatin than men ($P < 0.05$), which may be related to the higher sensitivity to platinum agents in women, but the exact mechanism is unknown. Imported and domestic oxaliplatin had no significant difference in the incidence of allergic reactions ($P > 0.05$), and no significant differences in age, body surface area, physical status (KPS score), tumor location, or pathologic type were detected between patients with and without allergic reactions. Statistical analysis on the above parameters were rare in published reports, both domestic and abroad, except that Lee *et al.*⁷ mentioned that the severity of hypersensitivity reactions caused by oxaliplatin did not seem to significantly correlate with the metastatic location of the tumor ($P = 0.15$).

The mechanisms of oxaliplatin hypersensitivity are not yet

entirely clear, while most studies suggest that it is related to a type-I hypersensitivity reaction.^{12,15} Our data showed that hypersensitivity reactions to oxaliplatin mostly occurred after previous use of oxaliplatin (the median course for allergic reaction was the 5th course) and allergic reactions occurred rapidly (within 5–360 min of oxaliplatin infusion), which fit the characteristics of type-I hypersensitivity reactions. Another study showed that oxaliplatin might act as a super-antigen to stimulate the proliferation and activation of T cells and cause the release of cytokines from the activated T cells (IL-6 and TNF- α).¹⁶ Another possible mechanism is that oxaliplatin binds to a major histocompatibility complex to mediate immune responses.¹³

In summary, this set of data indicated that the incidence of hypersensitivity reactions to oxaliplatin in Chinese patients with CRC was 11.9%, and grades I and II were the most common reactions while grade-III reactions were rare (1.8%) and grade-IV hypersensitivity reactions were not detected. Hypersensitivity reactions occurred in patients after multiple courses of oxaliplatin treatments, consistent with overseas reports, and no difference in oxaliplatin hypersensitivity reactions was detected among the Eastern and Western ethnic groups. Hypersensitivity reactions could remit after drug withdrawal and antiallergic treatment. The prophylactic application of antiallergic medication (5-hydroxytryptamine receptor I inhibitors and glucocorticoid) before future oxaliplatin chemotherapy could prevent the recurrence of allergy in some patients, but for those patients with previous life-threatening reactions, a change of chemotherapy programs might be the best choice.

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