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Original Article

Risk factors for oxaliplatin-induced hypersensitivity reaction in patients with colorectal cancer

Qiuyan Song[1*], Yuanxuan Cai[2*], Kangyuan Guo[3], Min Li[4], Zaoqin Yu[4], Qirui Tai[1], Yuhang Zhao[2], Xuan Zhu[5], Chengliang Zhang[4]

[1]Department of Pharmacy, The Sixth Affiliated Hospital of Kunming Medical University, Yuxi 653100, Yunnan, China; [2]School of Pharmacy, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China; [3]School of Medicine and Health Management, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China; [4]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei, China; [5]School of Computer, Central China Normal University, Wuhan 430079, Hubei, China. [*]Equal contributors.

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Abstract: Objective: Hypersensitivity reactions with oxaliplatin (OXA) have attracted much attention. This study aimed to analyze the risk factors for OXA-induced hypersensitivity reaction in Chinese colorectal cancer patients through a single-center retrospective investigation. Methods: The information from 459 colorectal cancer patients treated with OXA in a hospital was collected retrospectively to explore the risk factors for OXA-induced hypersensitivity reaction. Results: Among the 459 patients, 47 (10.24% incidence) cases developed hypersensitivity reactions, with a 3.70% incidence of grade III/IV reaction. The main symptoms included itching, flushing, dyspnea, and rash, which mainly involved skin and adnexa, respiratory system, and nervous system. Dexamethasone pretreatment presented no significant effects on the hypersensitivity reaction (P = 0.282). Multivariate analysis indicated that the previous allergic history (odds ratio (OR) 2.553, 95% confidence interval (CI) 1.139-5.721, P = 0.023) and OXA-free interval (OR 3.605, 95% CI 1.909-6.809, P = 0.000) were independent risk factors for OXA-induced hypersensitivity reaction. Conclusions: The incidence of OXA-induced hypersensitivity reaction in colorectal cancer patients was similar to those reported in other countries. Clinical medical staff should pay close attention to high-risk factors, such as allergic history and patients having OXA-free intervals in order to avoid or alleviate hypersensitivity reactions.

Keywords: Chinese population, multivariate analysis, allergic history, OXA-free interval

Introduction

Oxaliplatin (OXA) is one of the most widely used platinum drugs in clinical practice. It can cross-link with DNA through platinum atoms and affects DNA base pairing, replication, and gene transcription, thereby playing a cytotoxic role [1]. As a third-generation platinum drug, OXA is widely applied in clinical practice because of its excellent efficacy and anti-tumor activity. OXA-containing regimen is the first choice for a colorectal cancer treatment plan, and is recommended by the National Comprehensive Cancer Network (NCCN) of the USA. In addition, OXA also has good curative effects on liver cancer, gastric cancer, lymphoma, esophageal cancer, and head and neck tumors [2]. Common OXA-induced adverse reactions include neurotoxicity, hypersensitivity reaction, and cytopenia. (http://products.sanofi.us/eloxatin/eloxatin.pdf) However, reports on OXA-induced hypersensitivity reactions that might endanger life and seriously affect the safety and effectiveness of OXA, have been growing in recent years [3-9].

The administration of OXA causes hypersensitivity reactions in 2-25% of the cases, of which 1% of cases are severe [10-15]. Researchers have demonstrated the clinical characteristics and risk factors for OXA-induced allergic reaction in the European, Japanese, and American populations [12, 16, 17]. Previously, we also reported the clinical features of OXA-induced hypersensitivity reaction in Chinese patients by a retrospective multicenter analysis [18].

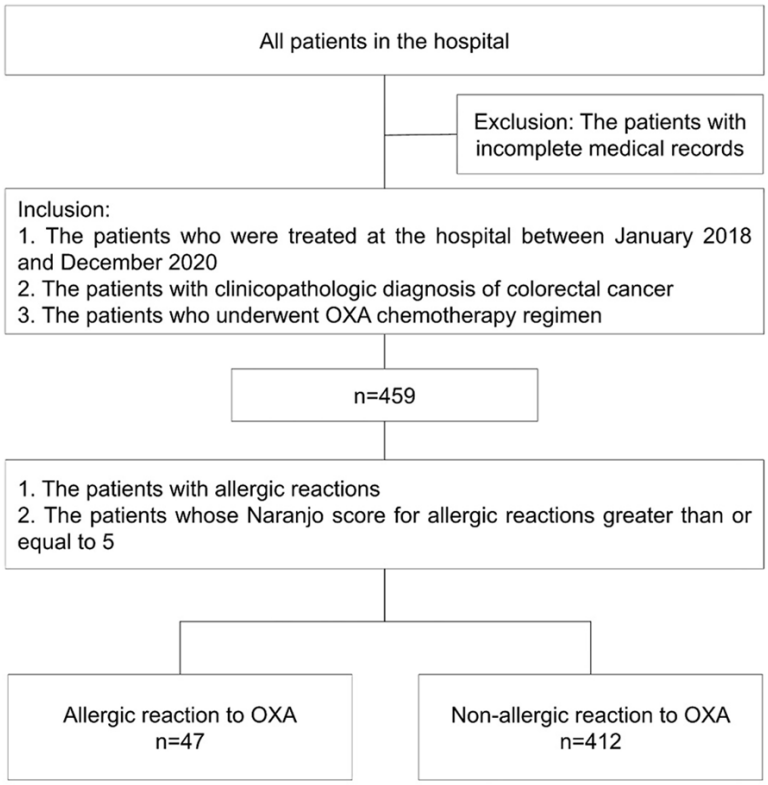

Figure 1. Screening process of the patients.

However, both our study and others' included a small sample size and studies in Chinese patients are lacking. In addition, dexamethasone is often used clinically to prevent OXA-induced hypersensitivity reaction, but its effects are still controversial. Therefore, in this study, a single-center retrospective investigation was conducted to analyze the risk factors of OXA-induced hypersensitivity reactions in Chinese colorectal cancer patients.

Materials and methods

The data were collected from the colorectal cancer patients treated with an OXA-based regimen in the Sixth Affiliated Hospital of Kunming Medical University from January 2018 to December 2020. Inclusion criteria were as follows: colorectal cancer patients who underwent OXA-based chemotherapy regimen; and whose hypersensitivity reactions during treatment were graded according to the Common Terminology Criteria for Adverse Events (CTCAE, version 5.0) and were considered to be OXA-induced after being judged by two physicians using the Naranjo evaluation method (Naranjo score of greater than or equal to 5) [19] (https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf). Exclusion criterion was patients with incomplete medical records. The study was approved by the Ethics Committee of the Sixth Affiliated Hospital of Kunming Medical University.

The gender, age, height, weight, allergic history, chemotherapy purpose, total chemotherapy cycles, chemotherapy regimen, a combination of targeted therapy, prophylactic use of dexamethasone, OXA-free interval, hypersensitivity reaction symptoms, hypersensitivity reaction grades, and other information of the patients were recorded. OXA-free interval was defined as the period between OXA withdrawal due to a stop-and-go strategy or the completion of adjuvant chemotherapy and the resumption of OXA [20].

Chi-square (χ^2) test (Fisher's exact test if necessary, for categorical variables) and Student's *t-test* (for continuous variables) were employed to compare and analyze the data. The multivariate logistic regression model was used to analyze the risk factors for OXA-induced hypersensitivity reaction. All statistical analyses were carried out using SPSS software (version 25.0, SPSS Inc., Chicago, IL, USA) and the *P*-value of < 0.05 was considered significant.

Results

Characteristics of patients

This retrospective study finally included 459 patients who underwent OXA chemotherapy. The screening process of the patients is shown in **Figure 1**.

Baseline characteristics of 459 patients are listed in **Table 1**. The patients included 309

Table 1. Baseline characteristics of research subjects

Characteristic		All	Non-hypersensitivity reaction	Hypersensitivity reaction	P
Age (year)	Mean	59.22	59.27	58.72	0.732[c]
	S.D.	10.44	10.58	9.23	
Gender, n (%)	Female	150 (32.68)	137 (33.25)	13 (27.66)	0.439[a]
	Male	309 (67.32)	275 (66.75)	34 (72.34)	
Height (cm)	Mean	167.98	167.88	168.84	0.435[c]
	S.D.	7.99	8.02	7.79	
Weight (kg)	Mean	61.70	61.60	62.62	0.345[c]
	S.D.	8.68	8.88	6.72	
Chemotherapy purpose, n (%)	Adjuvant chemotherapy	224 (48.80)	201 (48.79)	23 (48.94)	0.984[a]
	Palliative chemotherapy	235 (51.20)	211 (51.21)	24 (51.06)	
Total chemotherapy cycles	Mean	7.20	7.08	8.21	0.043[c,*]
	S.D.	3.63	3.62	3.61	
Chemotherapy regimen, n (%)	FOLFOX	247 (53.81)	216 (52.43)	31 (65.96)	0.188[d]
	XELOX	180 (39.22)	167 (40.53)	13 (27.66)	
	Others	32 (6.97)	29 (7.04)	3 (6.38)	
Allergy history, n (%)	No	414 (90.20)	377 (91.50)	37 (78.72)	0.011[b,*]
	Yes	45 (9.80)	35 (8.50)	10(21.28)	
Combination of targeted therapy, n (%)	No	420 (91.50)	376 (91.26)	44(93.62)	0.785[b]
	Yes	39 (8.50)	36 (8.74)	3 (6.38)	
Prophylactic use of Dexamethasone, n (%)	No	191 (41.61)	168 (40.78)	23 (48.94)	0.282[a]
	Yes	268 (58.39)	244 (59.22)	24 (51.06)	
OXA-free interval, n (%)	No	366 (79.74)	340 (82.52)	26 (55.32)	0.000[a,*]
	Yes	93 (20.26)	72 (17.48)	21 (44.68)	

Note: S.D., standard deviation; [a]Chi-square test; [b]Continuity Correction; [c]Student's t-test; [d]Fisher's exact test; [*]Statistically significant (P < 0.05).

males (67.32%) and 150 females (32.68%) with a mean age of 59.22 ± 10.44 years, an average height of 167.98 ± 7.99 cm, and an average weight of 61.70 ± 8.68 kg. A total of 224 patients underwent postoperative adjuvant chemotherapy and 235 patients underwent palliative chemotherapy after metastasis. The treatment cycles of the patients using the OXA-containing regimen numbered 1-20 cycles with an average of 7.20 cycles. The chemotherapy regimen of the patients included FOLFOX (combination of OXA, fluorouracil, and calcium folinate, such as FOLFOX4 and mFOLFOX6), XELOX (combination of OXA and capecitabine), and others (a combination of OXA and raltitrexed, and a combination of OXA and tegafur). Among the 459 patients, 247, 180, and 32 patients were treated with FOLFOX, XELOX, and other regimens, respectively. Among them, 45 (9.80%) patients had a history of drug-induced allergy and 39 (8.50%) of them were treated with a platinum-containing regimen as well as targeted therapy. 268 (58.39%) patients were intravenously injected with 5 mg of dexamethasone 30 min before the OXA infusion to prevent hypersensitivity reaction and 93 (20.26%) patients had a history of OXA-free intervals.

Hypersensitivity reactions

Among all the 459 patients, 47 developed OXA-induced hypersensitivity reactions, with an incidence rate of 10.24%; 17 patients developed severe hypersensitivity reaction (Grade III/IV), and 2 patients experienced an anaphylactic shock. Among the 47 allergic patients, 31 (65.96%) and 13 (27.66%) patients were administered the XELOX and FOLFOX regimens, respectively. The median cycle number of occurring hypersensitivity reactions was 7. The major clinical symptom of OXA-induced hypersensitivity reactions was skin itching, followed by flushing. dyspnea and rashes. Systemic involvements in the reaction included skin and its adnexa, respiratory system, nervous system, and gastrointestinal system. Detailed information related to the hypersensitivity reactions is listed in **Table 2**.

Table 2. Information on hypersensitivity reactions

Item		Count
Hypersensitivity reaction grades, n (%)	I	19 (40.43%)
	II	11 (23.40%)
	III	15 (31.91%)
	IV	2 (4.26%)
Chemotherapy regimen, n (%)	FOLFOX	31 (65.96%)
	XELOX	13 (27.66%)
	Others	3 (6.38%)
Cycle in which a hypersensitivity reaction occurs	Median	7
System-organ damage[a]	Skin and appendage disorders	pruritus (20), rash (14)
	Respiratory system disorders	dyspnea (14), larynx oedema (10), coughing (4)
	Autonomic nervous system disorders	flushing (17), hypotension (6), tachycardia (2), palpitation (2)
	Gastrointestinal system disorders	diarrhea (7), nausea (5), vomiting (4)
	Body as a whole-general disorders	anaphylactic shock (2), fever (2), rigors (2), sweating increased (1)
	Central and peripheral nervous system disorders	hypertension (2), dizziness (2), anesthesia local (1), tetany (1)
	Metabolic and nutritional disorders	oedema (4)
	White cell and res disorders	leucopenia (1)

Note: [a]World Health Organization Adverse Reaction Terms (WHO-ART) was used for system-organ damage and clinical manifestations.

Table 3. Results of multivariate logistic regression (Conditional forward)

Variable	OR (95% CI)	P
Allergic history	2.553 (1.139, 5.721)	0.023*
OXA-free interval	3.605 (1.909, 6.809)	0.000*
Constant	0.068	0.000*

Note: *Statistically significant (P < 0.05).

Analysis of the risk factors of hypersensitivity reactions

In order to analyze the risk factors for OXA-induced hypersensitivity reaction, the characteristics of patients with hypersensitivity reaction were compared with those without hypersensitivity reaction, as listed in **Table 1**. There was no significant difference between these two groups in gender, age, height, weight, chemotherapy purpose, and combination with targeted therapy. As compared to patients without dexamethasone pretreatment, no significant difference was found in the incidence of hypersensitivity reactions (P = 0.282) in those pretreated with dexamethasone. It was worth noting that, as compared with patients without hypersensitivity reaction, the patients with hypersensitivity reaction had a higher percentage of drug allergy history (21.28% VS. 8.50%, P = 0.011) and a greater number of chemotherapy cycles (8.21 VS. 7.08, P = 0.043). Furthermore, the hypersensitivity reaction rate in the patients with a history of OXA-free interval was higher than in those without OXA-free interval (44.68% VS. 17.48%, P = 0.000).

Multivariate logistic regression analysis

This study adopted the multivariate logistic regression model to analyze the risk factors related to OXA-induced hypersensitivity reaction. The conditional forward method was employed to input the variables, such as age, gender, height, weight, chemotherapy purpose, total chemotherapy cycles, chemotherapy regimen, allergy history, combination with targeted therapy, use of dexamethasone, and OXA-free interval, into the regression model for analysis. Finally, the allergy history and OXA-free interval were included in the equation. Logistic regression indicated that a history of allergy (history of allergy: odds ratio = 2.553, 95% confidence interval (CI) (1.139, 5.721), P = 0.023) and OXA-free interval (intermittent use of OXA: odds ratio = 3.605, 95% CI (1.909, 6.809), P = 0.000) were risk factors for an OXA-induced hypersensitivity reaction (**Table 3**).

Discussion

OXA is a third-generation platinum drug, widely used in the treatment of various cancers. In the past, it was thought that the dose-limiting toxicity of this drug, such as sensory neurotoxicity and neutropenia, had a significant impact on

its clinical application [21]. However, due to the increasing reports of OXA-induced hypersensitivity reactions, this side effect has gradually become an important reason for patients to terminate platinum-containing regimens. In an international multicenter phase III clinical trial (n = 1108), the incidence of OXA-induced hypersensitivity reactions was 10.3%, and that of Grade III/IV hypersensitivity reaction were 2.3% and 0.6%, respectively [22]. Yoshihiro reported that the incidence of OXA-induced hypersensitivity reaction in Japanese colorectal cancer patients was 17%, and that of grade III/IV hypersensitivity reaction was 5% [12]. The incidence of OXA-induced hypersensitivity reaction has usually been 10-25% in previous studies, and often occurred after the multi-cycle administration of OXA (median, 4-7 cycles) [7, 10, 11, 23, 24]. Sugihara found no racial difference in the incidence of hypersensitivity reaction by comparing the incidence of adverse reactions caused by FOLFOX4 treatment in two Asian and four western populations [25]. In this study, the incidence of OXA-induced hypersensitivity reaction in Chinese colorectal cancer patients was 10.24%, among which the incidence of grade III/IV hypersensitivity reaction was 3.70% and the median cycles of hypersensitivity reactions were 7. This was similar to previous reports, indicating that there might be no significant difference in the epidemiology of OXA-induced hypersensitivity reaction between Chinese colorectal cancer patients and those in other countries.

This study disclosed common clinical symptoms of OXA-induced hypersensitivity reaction, which included itching, flushing, dyspnea, and rash and this side effect mainly involved the skin and its adnexa, respiratory system, and nervous system. This result was similar to those reported in previous studies [10, 18, 26-28]. In the current study, most of the patients with hypersensitivity reaction had corresponding symptoms during the infusion of OXA, which quickly subsided after stopping the treatment, indicating that most of these reactions were type I hypersensitivity. The allergic symptoms in some patients lasted for a longer time and were similar to type II hypersensitivity, suggesting that OXA-induced hypersensitivity reaction may have many mechanisms.

The identification of risk factors for OXA-induced hypersensitivity reaction is crucial. Kim pointed out that young and female patients might be more prone to OXA-induced hypersensitivity reaction [1, 29]. In this study, the descriptive and multivariate logistic regression analyses showed that there was no significant difference in age and gender between patients with and without hypersensitivity reaction. Mori demonstrated that young patients and those with OXA-free intervals had a higher risk of developing a hypersensitivity reaction to OXA [30]. Seki showed that a history of drug and food allergies was a risk factor for OXA-induced hypersensitivity reaction [16]. Our study also found that the rate of hypersensitivity reaction in the patients who had previous allergic history and OXA-free interval was higher than in other patients ($P < 0.05$). Previous reports have shown that patients who used the OXA-containing regimen were more likely to develop hypersensitivity reaction along with an increase in chemotherapy cycles [5, 10]. In this study, although there were significant differences in the total number of cycles in the preliminary analysis, a null result was obtained by incorporating the number of cycles into the further analysis by logistic regression model. This might be due to the limited sample size of this study.

In this study, to avoid hypersensitivity reactions, 268 (58.4%) patients were administered 5 mg dexamethasone 30 min before the intravenous injection of OXA. However, logistic regression showed no significant difference in the incidence of hypersensitivity reaction between patients taking dexamethasone prophylactically and other patients. Siu also illustrated that the prophylactic use of dexamethasone could not effectively avoid OXA-induced hypersensitivity reaction [7, 31]. Yasuhiro pointed out that a high dose of dexamethasone could reduce the incidence of OXA-induced hypersensitivity reaction [32]. Yamauchi reported that the incidence of hypersensitivity reaction in the patients using less than 12 mg of dexamethasone prophylactically was significantly higher than those receiving more than 12 mg of dexamethasone [33]. The dose of dexamethasone in this study was only 5 mg, which might be insufficient to inhibit the allergic effects. Besides the dosage, the timing and treatment course of dexamethasone might also influence its inhibitory effect on OXA-induced hypersensitivity reaction. Therefore, the effectiveness of the prophylactic use of dexametha-

sone for OXA-induced hypersensitivity reactions still needs further study.

Numerous studies have demonstrated that platinum compounds can cause hypersensitivity reactions [28, 34-36]. At present, the mechanism of OXA-induced hypersensitivity reaction has not been clarified. The IgE-mediated type I hypersensitivity is considered the main cause of OXA-induced hypersensitivity reactions [37, 38]. Santini pointed out that T cell-mediated cytokine release was also a possible mechanism for OXA-induced hypersensitivity reaction. They observed an obvious increase in the levels of tumor necrosis factor-α and interleukin-6 in the patients with OXA-induced hypersensitivity reaction [39]. As this is a retrospective study, due to the lack of data on cytokine levels in patients, it was impossible to analyze the mechanism of OXA-induced hypersensitivity reaction.

To our knowledge, this study is the largest single-center study on the risk factors of OXA-induced hypersensitivity reaction. The results of multivariate analysis showed that a past allergy history and OXA-free interval were independent risk factors for OXA-induced hypersensitivity reaction. This suggests that clinicians should pay attention to the patients' previous medical history before using OXA, thereby ensuring safe medication of patients. However, there are some limitations to this study. Similar to other studies, the sample size in our study is still not large enough (459 cases), which might make it subject to sampling error. Because this study is a retrospective single-center study, the obtained case data may not provide all the information needed for the identification of risk factors, and the external validity of the conclusions may be relatively low. Thus, it will be meaningful to carry out more multi-center and actively monitored studies on the risk factors for OXA-induced hypersensitivity reaction.

Conclusions

The incidence of OXA-induced hypersensitivity reactions in colorectal cancer patients in China was 10.24%, which was similar to that reported in other countries. The preventative use of dexamethasone for OXA-induced hypersensitivity reaction needs further study. Clinical medical staff should pay close attention to high-risk factors, such as allergic history and patients with OXA-free intervals, in order to avoid or alleviate hypersensitivity reactions.

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Disclosure of conflict of interest

None.

Address correspondence to: Chengliang Zhang, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Avenue, Wuhan 430030, Hubei, China. Tel: +86-027-83663519; E-mail: clzhang@tjh.tjmu.edu.cn; Xuan Zhu, School of Computer, Central China Normal University, No. 152 Luoyu Road, Wuhan 430079, Hubei, China. E-mail: xuanzhu@mail.ccnu.edu.cn

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