

Clinical Features of Oxaliplatin-induced Hypersensitivity Reactions in Chinese Patients: A Retrospective Multicenter Analysis*

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[Abstract] Objective: The characteristics of oxaliplatin-induced hypersensitivity reactions (HSRs) in Chinese patients were investigated to provide a reference for patients treated with oxaliplatin. **Methods:** The study reviewed the records of patients who developed oxaliplatin-induced HSRs in 17 hospitals from May 2016 to May 2017. We collected and analyzed the basic information, history of oxaliplatin administration and premedication treatments, chemotherapy cycles, HSR symptoms, and the management and outcomes of these patients. **Results:** Oxaliplatin-induced HSRs were recorded in 137 patients who had been treated with oxaliplatin-containing regimens. Five different chemotherapy regimens were applied. The median infusion cycle when oxaliplatin-induced HSRs occurred was 7, and HSRs occurred during or shortly after oxaliplatin infusion. Most of the patients experienced grade 1 or grade 2 HSRs with mild symptoms of pruritis (49.64%), flushing (46.72%), chest discomfort (26.28%), and urticaria (25.55%). The majority of the patients completely recovered from HSRs following treatment with antihistamines and dexamethasone. Seven patients completed chemotherapy with oxaliplatin after the symptoms resolved with proper management. **Conclusion:** The results indicate that oxaliplatin-induced HSRs remain an important issue in safely and successfully fulfilling oxaliplatin-containing chemotherapy. Further studies are needed to analyze the risk factors and establish prophylaxis for such reactions.

Key words: oxaliplatin; hypersensitivity reaction; retrospective study; multicenter

Oxaliplatin, cisplatin, and carboplatin are categorized as platinum-containing agents and are widely used in cancer chemotherapy^[1, 2]. As third-generation platinum-containing chemotherapeutic agents, oxaliplatin contains a 1,2-diaminocyclohexane carrier ligand, which confers enhanced cytotoxicity and an altered drug resistance pattern compared to cisplatin and carboplatin^[3]. Currently, oxaliplatin is one of the core chemotherapeutic drugs for the treatment of locally developed colorectal carcinoma and pancreatic, gallbladder, and gynecologic cancers^[4, 5].

Oxaliplatin does not cause significant renal

impairment or ototoxicity and is considered to be a well-tolerated chemotherapeutic agent with a different toxicity profile compared to other platinum derivatives. Nonetheless, hypersensitivity reactions (HSRs) during oxaliplatin infusion are major problems associated with its application. With the expanded use of oxaliplatin for various malignancies, an increased number of HSRs have been reported, with an incidence of 8.9% to 23.8%^[1, 6]. Not only can hypersensitivity interrupt oxaliplatin infusion, but persistent severe HSRs can cause shock and death^[7]. However, studies on oxaliplatin-induced HSRs have largely been case reports or case series, and there are limited reports on the characteristics of patients with oxaliplatin-induced HSRs in China. This study determined the clinical features of oxaliplatin-induced HSRs in patients in China and provided a reference for medical workers.

1 PATIENTS AND METHODS

From May 2016 to May 2017, this study enrolled 137 patients from 17 hospitals in which oxaliplatin-

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induced HSRs developed. The data were obtained from electronic medical records using standardized data collection forms. The patient files were sufficiently documented to enable an analysis of the allergic reactions. We collected the following data: gender, age, known allergy to food or other drugs, type of cancer, treatment regimen, grade of the allergic reaction, the time of HSR occurrence, the cumulative dose of oxaliplatin (mg/m^2), the number of courses administered when the HSRs occurred, and the management strategies for and outcomes of the HSRs. We defined HSRs according to the common terminology criteria for adverse events (CTCAE), version 5.0. This study was approved by the Institutional Research Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

2 RESULTS

2.1 Patient Characteristics

Clinical information on the 137 patients (63 males and 74 females) is shown in table 1. The median age was 54 years old and the median Karnofsky (KPS) score was 90 points (range, 50–100 points). Oxaliplatin-containing chemotherapy was mostly used for colorectal cancer (58.39%), stomach cancer (13.14%), and ovarian cancer (13.14%). Only 14 patients had a prior history of allergies, and they were allergic to cephalosporin, penicillin, and metronidazole. One patient was allergic to mango. Of the oxaliplatin-based chemotherapy regimens, 84 patients were treated with the FOLFOX regimen, 31 patients with the TP regimen, 14 patients with the XELOX regimen, 5 patients with the SOX regimen, and 3 patients with the GEMOX regimen. Preventive premedications, such as diphenhydramine, promethazine, or dexamethasone were applied. Different doses of dexamethasone were given to 76 patients, and 22 patients used antihistamines (table 2).

Table 1 Baseline characteristics of the patients (n=137)

Characteristics	n	%
Male/female	63/74	NA
Median age [years (range)]	54 (22–75)	NA
Prior history of allergy		
Food	1	0.73
Drug	13	9.49
Cancer diagnosis		
Colorectal cancer	80	58.39
Stomach cancer	18	13.14
Ovarian cancer	18	13.14
Cervical cancer	7	5.11
Endometrial cancer	4	2.92
Fallopian tube cancer	2	1.46
Liver cancer	2	1.46
Others	6	4.38

NA: not applicable

Table 2 Treatment and premedication regimens

Subjects (total=137)		n (%)
Chemotherapy regimen		
	FOLFOX	84 (61.31)
	TP	31 (22.63)
	XELOX	14 (10.22)
	SOX	5 (3.65)
	GEMOX	3 (2.19)
Premedication		
Diphenhydramine	20 mg	5 (3.65)
	40 mg	13 (9.49)
Promethazine	25 mg	3 (2.19)
	50 mg	1 (0.73)
Diphenhydramine	20 mg	5 (3.65)
	40 mg	13 (9.49)
Promethazine	25 mg	3 (2.19)
	50 mg	1 (0.73)

2.2 Characteristics of Oxaliplatin-induced Hypersensitivity

The manifestations of hypersensitivity are shown in table 3. Pruritis (49.64%), flushing (46.72%), and rash (25.55%) were the most common events. The majority of the patients (88.32%) had HSRs of no more than grade 2. However, 16 patients experienced severe grade 3 or 4 HSRs. Five patients experienced anaphylactic shock. They all shared symptoms of dyspnea, dizziness, abdominal pain, and loss of consciousness from hypotension. The oxaliplatin-induced HSRs were observed at a median of 7 courses (range, 1–24) as shown in fig. 1, and the median cumulative dosage was $894.1 \text{ mg}/\text{m}^2$ (range, 100–5060 mg/m^2). According to our findings, only 3 patients experienced symptoms at the end of the infusion, while the others developed reactions mostly between 10 and 20 min from the start of the oxaliplatin infusion (fig. 2).

2.3 Management and Outcomes

Twenty patients with mild symptoms recovered without any treatment after discontinuation of the infusion and 7 patients completed following chemotherapy after the occurrence of HSRs (table 3). Most of the patients completely recovered

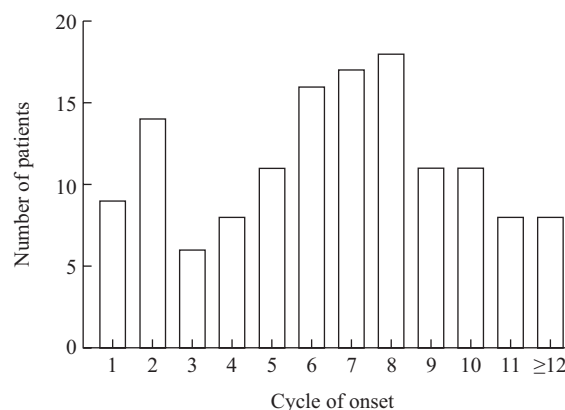


Fig. 1 Oxaliplatin infusion therapy cycles when the first HSRs occurred

from the HSRs with the use of antihistamines and dexamethasone. Some patients who developed severe reactions additionally required epinephrine and oxygen administration. All patients recovered after symptomatic therapy.

3 DISCUSSION

With the expanded use of oxaliplatin, more and

Table 3 Manifestations of oxaliplatin-induced HSRs

Manifestations	n (%)
Symptoms	
Cutaneous	
Rash/Urticaria	35 (25.55)
Pruritis	68 (49.64)
Flushing	64 (46.72)
Pallor	1 (0.73)
Digestive	
Nausea	28 (20.44)
Vomiting	19 (13.87)
Diarrhea	2 (1.46)
Neurologic	
Dizziness	6 (4.38)
Numb	26 (18.98)
Laryngeal abnormality	11 (8.03)
Loss of consciousness	8 (5.84)
Respiratory	
Dyspnea	21 (15.33)
Chest discomfort	36 (26.28)
Cough	3 (2.19)
Generalized	
Sweating	24 (17.52)
Chills	7 (5.11)
Fever	4 (2.92)
Pain	11 (8.03)
Cardiovascular	
Hypotension	10 (7.30)
Tachycardia	20 (14.59)
Vision	
Blurred vision	3 (2.19)
Conjunctival congestion	3 (2.19)
Sclera congestion	1 (0.73)
Anaphylaxis	5 (3.65)
Others	7 (5.11)
Severity grade	
1	22 (16.06)
2	99 (72.27)
3	11 (8.03)
4	5 (3.65)
Management	
Discontinuation of oxaliplatin administration	74 (54.01)
Injection of diphenhydramine	44 (32.12)
Intravenous dexamethasone	92 (67.15)
Oxygen administration	36 (26.28)
Subcutaneous adrenaline	6 (4.38)
Outcomes	
Successful completion of chemotherapy after HSRs	7 (5.11)
Symptoms improved or healed	137 (100)

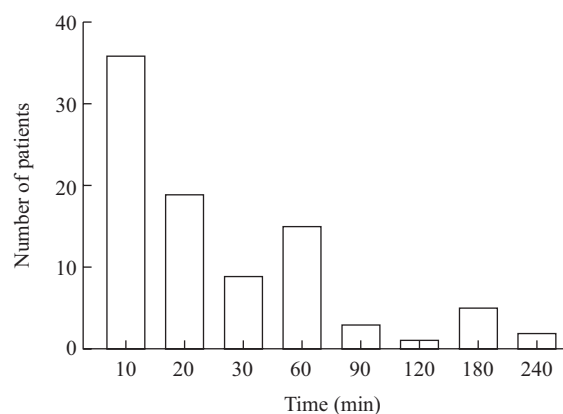


Fig. 2 Occurrence time of HSRs from the start of oxaliplatin infusion

more HSRs have been reported, and those are of major clinical concern. Even though most of the reactions are mild and curable, oxaliplatin-induced HSRs can be severe and life-threatening and are a significant cause of the discontinuation of treatment^[8]. Recently, a high frequency of severe cases of oxaliplatin-induced HSRs was documented^[9–11]. There have been limited reports on the clinical features of oxaliplatin-induced HSRs in China but such reports are important considering the extensive use of oxaliplatin. Current research showed that oxaliplatin-induced HSRs were associated with antigen-antibody reactions, which caused smooth muscle contractions, capillary dilation, and the release of inflammatory mediators from mast cells^[12]. However, the exact mechanisms of the allergic response and the pathophysiology of oxaliplatin-induced HSRs remain unclear and require further in-depth studies.

Drug reactions and food allergies have been reported as risk factors of oxaliplatin-induced hypersensitivity^[13]. However, Brian *et al* demonstrated that none of these factors were associated with hypersensitivity to oxaliplatin^[14]. We found only 15 patients with existing allergies to medications or food in our study. Therefore, we cannot conclude that previous allergies to medications or food were risk factors for oxaliplatin-induced anaphylaxis.

HSRs in patients receiving oxaliplatin often appeared after multiple therapeutic courses (median, 4–9 courses)^[15–17]. Our data suggest that HSRs occurred at a median of 7 courses of oxaliplatin chemotherapy, which is consistent with the evidence above. In addition, most allergic events in this study occurred within 10 min from the start of the infusion, which confirmed the results of Hiroaki^[18]. Thus, when patients receive oxaliplatin, close monitoring is needed during the entire infusion, particularly during the first 10 min and additional care should be taken after patients receive multiple courses of oxaliplatin.

The clinical manifestations of oxaliplatin-induced HSRs involve multiple systems and are variable

and unpredictable. The most common events were cutaneous symptoms, including pruritis (49.64%), flushing (46.72%), chest discomfort (26.28%), and urticaria (25.55%). With management that includes the discontinuation of oxaliplatin administration and injections of antihistamine drugs or intravenous dexamethasone, these mild symptoms can be resolved quickly. Moreover, these HSRs also occur in the digestive system, respiratory system, neurologic system, and cardiovascular system, which may require adrenaline treatment and oxygen administration. Considering all the possible consequences of oxaliplatin-induced HSRs, clinicians need to make a comprehensive judgment based on the time of oxaliplatin use and the symptoms of the patients and take appropriate and timely measures to deal with them.

Many studies do not recommend reintroducing oxaliplatin treatment in patients with severe hypersensitivity^[19-21]. Siu *et al* found that if patients developed a mild hypersensitivity reaction to oxaliplatin, they were more prone to developing grade 3 or 4 HSRs upon re-challenge^[22]. Two of our patients were re-administered with oxaliplatin and developed grade 3 HSRs with symptoms of dyspnea, hypotension, dizziness, and pain. Since the patients reacting to oxaliplatin had been treated with at least one dose of oxaliplatin^[15], and no standardized protocol for reintroduction is available, a careful balance of the risks and benefits must be considered for individual patients.

Given the number of rare and fatal HSRs that have occurred in recent years^[23-28], several protocols are currently in use to prevent them, such as premedication, skin testing, alteration of the infusion time, and desensitization. Kidera *et al* demonstrated that increased doses of dexamethasone and antihistamine significantly reduced oxaliplatin-related HSRs^[29]. However, the effect of premedication remains debatable as 72.27% of the patients were given premedications but still experienced HSRs in our study. Skin tests performed in patients that received at least 5 courses of oxaliplatin had good reliability in predicting HSRs^[30] but showed only 75% to 80% accuracy^[31]. It is worth noting that prolonging the time of infusion can help reduce hypersensitivity^[32, 33]. Desensitization therapy allows a small number of patients with previous HSRs to receive further oxaliplatin therapy and benefit from the drug^[34]. Many successful desensitization regimens have been used in the past decade^[18, 35, 36], but it is important to note that the risks and benefits must be weighed before offering desensitization procedures to patients.

Although we provided an overview of the epidemiologic and clinical features of oxaliplatin-induced HSRs in Chinese patients, its incidence could not be determined as the total number of oxaliplatin-

administered patients was unclear. The number of subjects in our study was also limited and we did not have control patients to compare HSR risks or the benefits of premedication. To resolve these problems, large-scale randomized controlled trials should be conducted in a broad population in the future.

In conclusion, this systematic study reported the characteristics of oxaliplatin-induced HSRs in Chinese patients and discussed the possible protocols to prevent HSRs. We also urge the medical staff to carefully monitor the entire infusion of oxaliplatin.

Conflict of Interest Statement

There is no conflict of interest in the submitted work.

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