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ORIGINAL ARTICLE

Intervention for oxaliplatin-induced hypersensitivity in China: a cross-sectional internet-based survey*

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Abstract

Objective This cross-sectional study aimed at investigating the intervention status and the influence of oncologists on oxaliplatin-induced hypersensitivity reactions (OIHR).

Methods Snowball sampling was used to send questionnaires to oncologists in various provinces and cities in China, via the internet, to collect data on their socio-demographic characteristics, the occurrence of OIHR, and the current status of interventions. One-way ANOVA and T-test of geographic samples were used to explore the relationship between the incidence of OIHR and intervention measures.

Results A total of 401 valid questionnaires were collected, most respondents were 30–40 years old, and most oncologists had 5 years of working experience. The proportions of glucocorticoid and H1 receptor antagonist use for OIHR prevention were 67.83% and 38.65%, respectively. The proportion of oncologists with longer working years and higher professional titles who used glucocorticoids for OIHR prevention was higher, and the observed OIHR incidence was lower. Pretreatment with glucocorticoids may be an effective preventive measure and can reduce the incidence of the OXA allergic reactions ($P < 0.05$).

Conclusion The risk awareness of junior oncologists to OIHR prevention should be strengthened, and clinical efficacy evaluation of glucocorticoids in OIHR prevention should be further promoted.

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Key words: oxaliplatin; hypersensitivity reactions; intervention; cross-sectional survey

Oxaliplatin (OXA), the third-generation platinum-containing chemotherapeutic agent, is wildly used for the treatment of colorectal cancers [1]. Its primary side effect is sensory neurotoxicity, and hematological and gastrointestinal toxicities. The high frequency of OXA use in gastrointestinal cancer patients has resulted in an increase in the reports of oxaliplatin-induced hypersensitivity reactions (OIHR), with the incidence increasing from < 1% to 23.8% [2–3]. Hypersensitivity reactions during oxaliplatin infusion can result in treatment discontinuation, which prolongs hospital stay and may be life threatening [4].

However, there are no optimal measures and suggestions for the prevention of such reactions. Furthermore, the exact mechanism of the pathophysiology of OIHR remains unclear. Glucocorticoids and H1 receptor antagonists have been the main drugs used to prevent this allergic reactions [5–6]; however, their effect remains unelucidated. Therefore, the present study aimed at investigating the current status of drug intervention for OIHR by oncologists, using questionnaires, and at providing references for clinicians.

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Materials and methods

Subjects

According to the principle that the selected subjects should be representative, this study distributed questionnaires to doctors engaged in tumor treatment in all provinces and cities of China through the Internet using snowball sampling, from September 1, 2019 to November 30. This study was approved by the Medical Ethics Committee of Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Methods

Data Measures

Self-designed questionnaires were designed by two experienced oncology pharmacists via literature review and clinical interviews on OIHR interventions. The questionnaire was comprised of three major sections. The first section provided to the participants the study purpose and method for filling the survey. The second section comprised of five items about the subject demographic characteristics, including age, gender, level of education, title, and working years. The third part enquired about specific usage of glucocorticoids and H1 receptor antagonists, and the incidence of OIHR observed by subjects. The incidence of OIHR was assigned 1, 2, 3, 4, and 5 points for "≤ 1%", "1%–3%", "3%–5%", "5%–10%", and "≥ 10%", respectively, and the mean value was calculated. The statistical results were expressed as ($\bar{\chi}$ ± SD) values, and a higher value meant a higher incidence.

Statistical analysis

Epi Data version 3.1 (USA) was used for data entry, and the data collected were analyzed using IBM Statistical Package for Social Sciences version 19.0 (SPSS Inc., Chicago, IL, USA). Both descriptive and inferential statistics were applied for data analyses. We describe the demographic characteristics of oncologists, premedication for OIHR, and the average score for OIHR incidence. Besides, the Chi-square test, One-way ANOVA, and T-test were used to analyze the association between OIHR preventive drug use and OIHR occurrence. All tests were two-sided, and a P value < 0.05 was considered statistically significant.

Results

Study subject characteristics and prophylactic medication status

A total of 416 questionnaires were issued and 401 valid questionnaires were collected from 31 provinces or administrative regions of China, except Qinghai, Ningxia, and Taiwan, with a response rate of 96.39%. Women accounted for a large proportion (61.10%) of the 401 oncologists.

Approximately 32.92% of the subjects were under 30 years old, 176 (43.89%) were 30–40 years old, and 93 (23.19%) were over 40 years old. Among them, 52.12% of the oncologists had been engaged in tumor work for less than 5 years, 19.20% had been engaged for 5–10 years, and 28.68% had been engaged for more than 10 years. A total of 217 persons had bachelor's degrees or less (54.11%), 159 had master degrees (39.65%), and 25 had doctorates (6.24%); 106 (26.43%) oncologists were juniors, 217 (54.11%) were intermediates, and 78 (19.46%) were seniors (Table 1).

Among the respondents, 272 oncologists (67.83%) used glucocorticoids for OIHR prevention, 155 (38.65%) used H1 receptor antagonists for intervention, 29.92% used both glucocorticoids and H1 receptor antagonists, and 23.44% administered no preventive therapy. Oncologists with more than 10 years (P = 0.015) experience and at least senior titles (P = 0.040), tended to use glucocorticoids as intervention for OIHR, whereas those with junior titles tented to use H1 receptor antagonists (Table 1).

Subject demographic characteristics and OIHR incidence

There were no statistically significant differences between the gender, age, and educational level of the participating oncologists and the observed OIHR incidence (P = 0.225, 0.765, and 0.784, respectively). However, the working years and professional title of the medical staff significantly affected the observed incidence (P = 0.009, 0.041, respectively) (Table 2).

Interventions and OIHR incidence

The average score of the above mentioned conditions and the OIHR incidence were statistically analyzed among oncologists who used glucocorticoids and H1 receptor antagonists alone for OIHR prevention, as well as the combination or no drug intervention. The results showed that the P values of the combination of both drugs, or glucocorticoids and H1 receptor antagonists alone, were 0.043, 0.044, and 0.096, respectively, compared with no preventive drug use (Table 3). The results demonstrated that premedication with glucocorticoids before chemotherapy, either alone or in combination with H1 receptor antagonists, could reduce the incidence of OXA allergic reaction to a certain extent.

Discussion

OXA, a third-generation platinum drug, is extensively used for the treatment of gastrointestinal cancers and other tumors, due to its low toxicity and broad anti-tumor spectrum [7]. Nevertheless, OIHR can lead to chemotherapy discontinuation and a poor quality of life, thus posing a potential threat to cancer patients [8]. Symptoms of

Table 1 Study subject characteristics and OIHR prophylactic medication status

Characteristics (*n*)	The usage of glucocorticoids			The usage of H1 receptor antagonists		
	n (%)	χ^2	*P*	*n* (%)	χ^2	*P*
Gender						
Male (156)	100 (64.10)	0.024	0.877	55 (35.26)	0.656	0.418
Female (245)	172 (70.20)			100 (40.82)		
Age (years)						
≤ 30 (132)	90 (68.18)	2.652	0.266	48 (36.36)	1.056	0.590
30–40 (176)	125 (71.02)			73 (41.48)		
≥ 40 (93)	57 (61.29)			34 (36.56)		
Working years						
≤5 (209)	130 (62.20)	8.373	0.015*	82 (39.23)	0.741	0.690
5–10 (77)	54 (70.13)			32 (41.56)		
≥ 10 (115)	88 (76.52)			41 (35.65)		
Educational level						
Bachelor and below (217)	140 (64.52)	3.285	0.194	96 (44.24)	0.726	0.696
Masters (159)	112 (70.44)			54 (33.96)		
Doctor (25)	20 (80)			5 (20)		
Title						
Junior and below (106)	63 (59.43)	6.437	0.040*	41 (38.68)	0.726	0.696
Intermediate (217)	151 (69.59)			87 (40.09)		
Senior (78)	58 (74.36)			27 (34.62)		

* $P < 0.05$

OIHR range from cutaneous reactions such as flushing, pruritus, and urticarial, to life-threatening respiratory and cardiovascular conditions such as anaphylactic shock, acute hemolysis, and thrombocytopenia [9].

Table 2 Subject basic information and average OIHR score

Demographic characteristics (*n*)	Average score of OXA allergic reaction rate ($\bar{\chi}$ ± SD)	F/t	P
Gender			
Male (156)	2.41 ± 0.90	0.858	0.225
Female (245)	2.33 ± 0.91		
Age (years)			
≤ 30 (132)	2.40 ± 0.84	0.260	0.765
30–40 (176)	2.36 ± 0.91		
≥ 40 (93)	2.31 ± 0.99		
Working years			
≤ 5 (209)	2.49 ± 0.84	4.788	0.009*
5–10 (77)	2.17 ± 0.90		
≥ 10 (115)	2.25 ± 0.99		
Educational level			
Bachelor and below (217)	2.38 ± 0.93	0.243	0.784
Masters (159)	2.32 ± 0.88		
Doctor (25)	2.44 ± 0.82		
Title			
Junior and below (106)	2.45 ± 0.77	4.277	0.041*
Intermediate (217)	2.21 ± 0.98		
Senior (78)	2.14 ± 0.96		

* $P < 0.05$

Currently, the mechanism of OIHR remains unelucidated. However, the mechanism underlying hypersensitivity to OXA is reportedly associated with immunoglobulin E (IgE)-mediated hypersensitivity [10–11]. Domestic and foreign literature have reported that OIHR often occurs after multi-cycle chemotherapy [12–13], and that a few patients develop allergic reactions at first OXA infusion. This suggests that OIHR can occur at any chemotherapy cycle. At present, there are no effective measures for preventing and treating OIHR. Premedication, prolonged OXA infusion time, and desensitization therapy may reduce the occurrence of these reactions [14–15]. Most physicians use glucocorticoids and histamine receptor antagonists for OIHR prevention [16–17]. Glucocorticoid is the most important stress-regulating hormone in the body, and is also the most widely clinically used and effective anti-inflammatory and immunosuppressant agent. Dexamethasone is the most common glucocorticoid used for hypersensitivity intervention. H1 receptor antagonists mainly prevent histamine production by acting on target cells through reversible competition for histamine receptor sites on cells, thus blocking H1 receptors to play an anti-allergy role. Additionally, promethazine and diphenhydramine are the most commonly used histamine receptor antagonists.

However, the current situation of drug intervention for OIHR prevention in China remains unknown. This

Table 3 Interventive measures and OIHR incidence

Interventive measures	*n* (%)	Average score of OXA allergic reaction rate ($\bar{\chi}$ ± SD)	F/t	*P*	*P* [a]
Combination of glucocorticoid and H1 receptor antagonist	120 (29.92)	2.26 ± 0.96	2.056	0. 015	0.043*
Glucocorticoid alone	152 (37.90)	2.27 ± 0.92			0.044*
H1 receptor antagonist alone	35 (8.73)	2.50 ± 0.71			0.906
No drug intervention	94 (23.44)	2.52 ± 0.97			

Compared with no drug intervention, * $P < 0.05$

cross-sectional study involved the distribution of a survey to clinical oncologists on the current status of OIHR interventions. The study also analyzed the factors that may affect the incidence of these reactions, so as to provide references for oncologists. The results showed that 76.56% of oncologists had adopted interventions: 67.83% used glucocorticoids for OIHR prevention, while 38.65% used H1 receptor antagonists. Moreover, a few oncologists used both drugs. Additionally, oncologists with longer working years and a higher professional title better adapted to intervention with glucocorticoid, and observed a lower incidence of OXA allergic reactions. Therefore, it is necessary to strengthen risk awareness training for less experienced oncologists with lower titles, to enhance their knowledge on OIHR prevention.

Some oncologists used a combination of both drugs for prevention. Thus, the difference between the effects of glucocorticoids and H1 receptor antagonists alone and that of the combination in OIHR prevention, were analyzed. The analysis showed that glucocorticoids might effectively reduce the incidence of allergic reactions. We concluded that oncologists in China were not only inclined to use glucocorticoids for OIHR prevention, but that the observed incidence of the reactions was lower with their use, indicating premedication with glucocorticoids might be an effective way of preventing OIHR.

Although this study analyzed the intervention status of OIHR and the potential effect, it had the following limitations. First, although we collected 401 questionnaires which can be reflective of the situation in the country to some extent, some provinces were not covered, and there were differences in the number of questionnaires completed by each provinces, inevitably introducing bias. Furthermore, the study investigated OIHR incidence via the personal experiences of the respondents, rather than the real clinical incidence of OIHR, introducing bias owed to subjectivity. Further, different strains of glucocorticoids and H1 receptor antagonists are used for prevention, and the doses and frequency used by each oncologist may be different. Therefore, this paper failed to properly evaluate the different treatment strategies applied by oncologists. These establish the need for further analytical research with a larger sample size.

In conclusion, this paper investigated the OIHR interventions of oncologists in China, which can reflect their knowledge and application of OIHR treatment options to some extent. Furthermore, it provides reference for physicians for the need to further enhance their cognition of OIHR treatment and prevention, to enhance safe clinical OXA use.

Conflicts of interest

The authors indicated no potential conflicts of interest.

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