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Analysis of Adverse Drug Reactions with Oxaliplatin-Based Hepatic Arterial Infusion Chemotherapy

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Abstract: Objectives: To analyze the clinical characteristics and factors associated with adverse drug reactions (ADR) in liver cancer patients receiving oxaliplatin-based hepatic arterial infusion chemotherapy (HAIC). **Methods**: A retrospective analysis was performed on the clinical data of 137 patients with liver cancer who received oxaliplatin-based HAIC. Changes in baseline characteristics, inflammatory factors, and other laboratory indicators in the no-ADR and ADR groups were analyzed. **Results**: The incidence of serious ADR (CTCAE ≥ 3) was 21.9% (30/137). There was no significant difference in the cumulative dose of oxaliplatin between the two groups [157.3 (80.3, 322.4) vs. 206.6 (139.1, 324.2), P=0.161]. The increase in NEUT and IL-6 was greater in the group treated with ADR than in the group not treated with ADR. Changes in NEUT [4.1 (1.5, 6.2) vs. 2.5 (0.5, 4.9), P=0.045] and changes in NEUTIL-6 [4.2 (-0.2, 22.9) vs. 0.8 (-3.9, 7.7), P=0.026]. TBIL, ALT, AST, ALP, WBC, NEUT, PCT, CRP, TNF, IL-2R, IL-6, and IL-10 were significantly higher after treatment than before in the ADR group ($P < 0.05$). In contrast, ALB and AFP were decreased. **Conclusions**: The severe ADR (CTCAE ≥ 3) associated with oxaliplatin-based HAIC may be closely related to increased inflammatory factors such as NEUT and IL-6. We should be vigilant for allergic reactions to oxaliplatin and increase monitoring during treatment.

Keywords: oxaliplatin; hepatic arterial infusion chemotherapy; adverse drug reactions

1. Introduction

Currently, over 50% of the global population of liver cancer patients resides in China. Liver cancer is the fourth leading cause of cancer, and the second fatality rate in China[1,2]. The most prevalent transarterial interventions for liver cancer are hepatic arterial infusion chemotherapy (HAIC), transarterial chemoembolization (TACE)[3]. HAIC is a transarterial treatment that directly delivers chemotherapeutic agents into tumor-associated hepatic arterial branches to increase local concentrations, and thus effectively reduce the tumor burden with lower systemic toxicity through a greater first-pass effect in the liver[4]. The advantages of HAIC include increased local drug concentration and enhanced uptake of drug by the tumor. HAIC has been demonstrated to be an efficacious treatment for advanced or metastatic liver cancer, and has been endorsed in multiple guidelines for the management of liver cancer[5–9]. In recent years, the innovative oxaliplatin-based HAIC regimen, which has been adopted by scholars in China, has resulted in a notable improvement in both the tumor response rate and the patient survival rate[4,10–13].

Nevertheless, the factors that impact the safety of oxaliplatin-based HAIC therapy in clinical practice have yet to be documented. The objective of this study is to examine the clinical characteristics and contributing factors of adverse drug reactions (ADR) associated with oxaliplatin-based HAIC therapy in liver cancer patients, which is beneficial to strengthen the monitoring of ADR and improve the safety of antitumor therapy.

2. Materials and Methods

This retrospective cohort study included 137 liver cancer patients who received oxaliplatin-based HAIC therapy from January 2021 to December 2023 at our institution, Zhongshan Hospital

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(Xiamen), Fudan University. Patients clinically diagnosed with primary or secondary liver cancer[3,14] and not contraindicated for HAIC. Patients were excluded if baseline echocardiography, serious adverse drug reaction (CTCAE ≥ 3)[15] within 3 months before HAIC.

Patient demographics (age, sex, BMI, hepatitis B virus, TACE treatment, complication, and laboratory tests) were collected from the hospital's medical record system. Liver function includes: total bilirubin (TBIL), albumin (ALB), alanine aminotransferase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), glutamyl transferase (GGT). Renal function includes: creatinine (Cr), estimated glomerular filtration rate (EGFR). Inflammatory factors include: white blood cell (WBC), neutrophilic granulocyte (NE), procalcitonin (PCT), c-reactive protein (CRP). Cytokines include: trumor necrosis factor (TNF), interleukin-1β (IL-1β), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10). Liver cancer tumor marker is alpha-fetoprotein (AFP).

The ADR group was defined as discontinuation of oxaliplatin-based HAIC therapy due to an ADR (CTCAE ≥ 3). In contrast, the no-ADR group had no adverse events or interruptions. The clinical manifestations of adverse reactions, the duration of administration, and the laboratory test results were recorded in detail. The relevant laboratory indices were monitored before the treatment and on the first day after HAIC.

Continuous variables were expressed as mean and standard deviation (SD) or M (P25, P75). Pearson's chi-squared and Fisher's exact test were used to compare categorical data. Continuous variables were tested using Student's t test and Mann–Whitney U test. The Mann–Whitney U test was chosen to determine differences in continuous data for non-parametric variables. $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS 23.0 software.

3. Results

3.1. Demographic Data

Demographic details of the study participants are shown in Table 1. A total of 137 patients with liver cancer were included, with a mean age of 56.2±1.09 years, 119 (86.9%) males, 104 (75.9%) HBsAg (positive), and a history of previous TACE treatment in 92 (67.2%). ADR group were 30 cases and no-ADR group were 107 cases, and there was no significant difference in pre-treatment demographics between the two groups.

Table 1. Demographic characteristics.

Characteristics	no-ADR (n=107)	ADR (n=30)	*p*-Value
Age/years	56.9±12.5	53.8±13.8	0.228[c]
Sex(Male)/(n, %)	94 (87.9)	25 (83.3)	0.545[b]
BMI/kg·m^{-2}	22.1±3.18	22.1±3.79	0.938[c]
HBsAg (Positive)/(n, %)	82 (76.6)	22 (73.3)	0.709[a]
TACE treatment/(n, %)	73 (68.2)	19 (63.3)	0.614[a]
Complication/(n, %)			
Hypertension	32 (29.9)	10 (33.3)	0.719[a]
Diabetes	15 (14.0)	5 (16.7)	0.771[b]
Coronary heart disease	4 (3.7)	0	0.576[b]
Smoking history	18 (16.8)	6 (20)	0.686[a]
Drinking history	14 (13.1)	5 (16.7)	0.565[b]
Liver function			
TBIL/μmol·L^{-1}	12.5 (7.1, 18.7)	9.1 (7.3, 14.0)	0.177[d]
ALB/g·L^{-1}	39.49±5.03	40.60±6.64	0.325[c]
ALT/U·L^{-1}	36.0 (25.0, 56.0)	43.5 (26.0, 58.8)	0.725[d]
AST/U·L^{-1}	58.0 (40.0, 86.0)	54.5 (39.3, 77.0)	0.666[d]

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ALP/U·L^{-1}	164.0 (107.0, 229.0)	162.5 (128.0, 193.0)	0.789[d]
GGT/U·L^{-1}	162.0 (67.0, 331.0)	124.0 (90.5, 226.8)	0.505[d]
Renal function			
Cr/μmol·L^{-1}	72.0 (59.0, 87.0）	75.0 (66.0, 88.3)	0.378[d]
EGFR/mL·min^{-1}·1.73m^{-2}	98.0 (80.2, 108.0)	96.9 (79.4, 108.7)	0.996[d]
Inflammatory factors			
WBC/10^{9}·L^{-1}	6.08±2.17	5.95±2.25	0.765[c]
NEUT/10^{9}·L^{-1}	3.89±1.69	3.71±1.87	0.614[c]
PCT/ng·mL^{-1}	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.944[d]
CRP/mg·L^{-1}	11.5 (4.4, 29.0)	7.2 (3.4, 25.2）	0.274[d]
Cytokines			
TNF/pg·ml^{-1}	9.8 (6.8, 13.9)	10.1 (6.9, 14.8)	0.698[d]
IL-1β/pg·ml^{-1}	5.0 (5.0, 5.0)	5.0 (5.0, 5.9)	0.653[d]
IL-2R/U·mL^{-1}	578.0 (444.0, 804.0)	618.0 (457.5, 802.0)	0.749[d]
IL-6/pg·ml^{-1}	8.4 (4.6, 14.8)	4.6 (3.4, 16.6)	0.086[d]
IL-8/pg·ml^{-1}	33.2 (15.4, 67.1)	32.2 (18.8, 58.5)	0.402[d]
IL-10/pg·ml^{-1}	5.0 (5.0, 5.0)	5.0 (5.0, 5.0)	0.431[d]
AFP/ng·ml^{-1}	358.0 (6.3, 10649.0)	65.7 (4.9, 959.8)	0.326[d]
Dose of oxaliplatin cumulative/mg·m^{-2}	157.3 (80.3, 322.4)	206.6 (139.1, 324.2)	0.161[d]

[a]Pearson's chi-square test, [b] Fisher's exact test, [c] Student's t test, [d] Mann–Whitney U test.

3.2. Change Before and After Treatment

Changes in laboratory indices liver function, renal function, inflammatory factors and cytokines are shown in Table 2. Changes were expressed as the difference between the post-treatment minus the pre-treatment. The NEUT increased more in the ADR group than in the non-ADR group [4.1 (1.5, 6.2) vs. 2.5 (0.5, 4.9), P=0.045]. Similarly, changes in IL-6 increased in the ADR group compared to the no-ADR group [4.2 (-0.2, 22.9) vs. 0.8 (-3.9, 7.7), P=0.026].

Table 2. Comparison of the changes in the two groups before and after the treatment.

Laboratory Indicators	no-ADR (n=107)	ADR (n=30)	*p*-Value
Liver function			
TBIL/μmol·L^{-1}	2.4 (-1.3, 8.2)	0.8 (-0.8, 4.9)	0.426
ALB/g·L^{-1}	-4.0 (-7.0, -1.0)	-5.0 (-10.3, -1.8)	0.181
ALT/U·L^{-1}	4.0 (-5.0, 27.0)	13.5 (-5.3, 61.3)	0.169
AST/U·L^{-1}	12.0 (-6.0, 63.0)	14.5 (-5.0, 66.8)	0.901
ALP/U·L^{-1}	-14.0 (-49.0, 2.0)	-13.0 (-62.0, 3.5)	0.944
GGT/U·L^{-1}	-12.0 (-81.0, 4.0)	-10.5 (-83.5, 56.3)	0.645
Renal function			
Cr/μmol·L^{-1}	-7.0 (-14.0, 2.0)	-3.5 (-14.0, 6.8)	0.138
EGFR/mL·min^{-1}·1.73m^{-2}	5.0(-2.0, 10.7)	1.4 (-10.4, 10.0)	0.132
Inflammatory factors			
WBC/10^{9}·L^{-1}	2.1 (-0.2, 4.3)	2.6 (0.9，4.7)	0.173
NEUT/10^{9}·L^{-1}	2.5 (0.5, 4.9)	4.1 (1.5, 6.2)	0.045*

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PCT/ng·mL^{-1}	0.0 (0.0, 0.1)	0.0 (0.0, 0.3)	0.254
CRP/mg·L^{-1}	-0.7 (-7.4, 10.5)	-0.6 (-5.6, 16.1)	0.595
Cytokines			
TNF/pg·ml^{-1}	2.7 (0.4, 11.3)	4.3 (-0.1, 21.5)	0.457
IL-1β/pg·ml^{-1}	0.0 (0.0, 2.3)	0.0 (0.0, 2.2)	0.679
IL-2R/U·mL^{-1}	93.0 (-31.0, 269.0)	35.5 (-8.5, 262.0)	0.876
IL-6/pg·ml^{-1}	0.8 (-3.9, 7.7)	4.2 (-0.2, 22.9)	0.026*
IL-8/pg·ml^{-1}	5.1 (-9.8, 55.3)	-4.4 (-33.3, 24.9)	0.069
IL-10/pg·ml^{-1}	0.0 (0.0, 0.0)	0.0 (0.0, 2.7)	0.054
AFP/ng·ml^{-1}	-0.3 (-24.1, 1.0)	-9.0 (-63.8, 0.7)	0.159

* the level of significant different <0.05.

3.3. ADR Group Pretreatment vs. Posttreatment

Liver function, renal function, inflammatory factors, and cytokines before and after treatment in the ADR group are shown in Table 3. TBIL, ALT, AST, ALP, WBC, NEUT, PCT, CRP, TNF, IL-2R, IL-6, and IL-10 were higher after oxaliplatin-based HAIC treatment ($P < 0.05$). ALB, AFP lower than pretreatment values ($P < 0.05$).

Table 3. Laboratory indicators before and after treatment in the ADR group.

Laboratory Indicators	Pre-treatment	Post-treatment	*p*-Value
Liver function			
TBIL/μmol·L^{-1}	9.4 (7.9, 12.6)	13.0 (9.6, 116.4)	<0.001*
ALB/g·L^{-1}	41.0 (37.0, 44.0)	35.0 (32.8, 39.0)	<0.001*
ALT/U·L^{-1}	41.5 (23.3, 56.3)	62.5 (36.8, 99.0)	0.002*
AST/U·L^{-1}	48.0 (31.5, 75.3)	80.5 (48.5, 122.8)	0.001*
ALP/U·L^{-1}	120.0 (84.8, 165.5)	97.0 (69.3, 142.5)	0.009*
GGT/U·L^{-1}	116.0 (75.5, 173.5)	131.0 (71.3, 188.3)	0.787
Renal function			
Cr/μmol·L^{-1}	78.5 (66.8, 83.8)	67.0 (58.8, 81.5)	0.531
EGFR/mL·min^{-1}·1.73m^{-2}	97.1 (83.8, 111.3)	100.5 (78.6, 119.0)	0.516
Inflammatory factors			
WBC/10^{9}·L^{-1}	5.1 (4.5, 6.2)	9.0 (6.5, 11.4)	<0.001*
NEUT/10^{9}·L^{-1}	2.9 (2.1, 4.1)	7.9 (5.5, 10.0)	<0.001*
PCT/ng·mL^{-1}	0.1 (0.0, 0.2)	0.2 (0.1, 0.6)	<0.001*
CRP/mg·L^{-1}	3.3 (1.3, 12.4)	13.6 (1.8, 32.4)	0.022*
Cytokines			
TNF/pg·ml^{-1}	10.1 (6.8, 14.8)	17.5 (10.2, 30.2)	0.001*
IL-1β/pg·ml^{-1}	5.0 (5.0, 5.9)	5.0 (5.0, 8.2)	0.136
IL-2R/U·mL^{-1}	618.0 (457.5,802.0)	683.0 (462.8,1116.5)	0.021*
IL-6/pg·ml^{-1}	4.6 (3.4, 16.6)	9.4 (5.2, 39.3)	0.010*
IL-8/pg·ml^{-1}	32.2 (18.8, 58.5)	35.6 (19.8, 102.6)	0.572
IL-10/pg·ml^{-1}	5.0 (5.0, 5.0)	5.0 (5.0, 7.7)	0.015*

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AFP/ng·ml^{-1}	51.1 (6.7, 714.3)	40.1 (5.7, 323.3)	0.007*

* the level of significant different <0.05.

3.4. Clinical Characteristics of ADR Group

Clinical characteristics of ADR group adverse reactions are shown in Table 4. The incidence of ADR (CTCAE ≥ 3) was 21.9% (30/137) and there were no HAIC procedure-related adverse events such as catheter dislodgement and catheter occlusion.

Integumentary system manifested as rash and pruritus was seen in 10 cases (33.3%). Digestive system manifestations of abdominal pain, severe vomiting, intestinal torsion 6 cases (20.0%). Circulatory system related manifestations were fever and chills, dyspnea, hypotension, dizziness, and headache in 15 cases (50.0%). Hematologic manifestations in 5 cases (16.7%) were myelosuppression such as leukopenia, neutropenia, and thrombocytopenia. Adverse reactions involved 2 systems in 6 patients, others single.

Targeted drugs in the anti-tumor combination regimen include lenvatinib, bevacizumab, apatinib and regorafenib. Immunotherapy drugs are mainly PD-1 inhibitors such as Tislelizumab, Sintilimab, Camrelizumab, Toripalimab, Pembrolizumab and Nivolumab.

Table 4. Clinical characteristics of ADR group (n=30) adverse reactions.

Clinical characteristics	ADR (n=30)
ADR-involved systems/(n, %)	
Integumentary system	10 (33.3)
Digestive system	6 (20.0)
Circulatory system	15 (50.0)
Hematologic system	5 (16.7)
HAIC treatment	
Treatment cycle/n	3.0 (1.8, 4.0)
Date of ADR response/d	58.0 (31.3, 92.3)
Dose of oxaliplatin cumulative/mg·m^{-2}	206.6 (139.1, 324.2)
RALOX/(n, %)	9 (30.0)
GEM0X/(n, %)	3 (10.0)
FOLFOX/(n, %)	18 (60.0)
Comprehensive treatment/(n, %)	
Combined targeted therapy	7 (23.3)
Combined immunotherapy	2 (6.7)
Combined targeted and immunotherapy	21 (70.0)

4. Discussion

Currently, oxaliplatin-based FOLFOX (oxaliplatin, leucovorin Folinate, fluorouracil) is the mainstay HAIC regimen in China. It is also approved to treat locally advanced and metastatic liver cancer that is not surgically resectable[3]. RALOX (oxaliplatin, raltitrexed), GEM0X (oxaliplatin, gemcitabine) are other oxaliplatin-based HAIC regimens. HAIC procedure-related ADRs, infusion-related reactions, and drug-related toxicities are complications of HAIC therapy[13,16].

Although HAIC therapy is a minimally invasive and relatively safe treatment modality, the factors influencing its adverse effects have not been clearly demonstrated. The incidence of ADR (CTCAE ≥ 3) with FOLFOX-based HAIC therapy has been reported to be approximately 34.2%, mainly in the form of myelosuppression and gastrointestinal reactions[17,18]. In our study, 21.9% (30/137) of patients developed severe ADR (CTCAE ≥ 3), of which 5 (16.7%) developed severe myelosuppression and 11 (36.7%) were acutely sensitized to oxaliplatin. There were 10 patients with oxaliplatin allergy who presented with severe rash and pruritus, and 1 patient who presented with

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severe dyspnea and decreased blood pressure. Fourteen patients developed febrile chills (temperature ≥ 38.5℃), resulting in interruption of HAIC therapy and prolonged hospitalization. In the treatment of HAIC, we analyzed the possible association of serious ADRs with oxaliplatin. Though oxaliplatin is a third-generation platinum that is highly effective, less toxic, and less likely to develop resistance, it still carries the risk of allergic reactions, myelosuppression, and gastrointestinal toxicity[19].

Oxaliplatin's black box warning states that serious allergic reactions can be fatal and that there is no effective way to predict or prevent these serious adverse reactions[20]. The study reported that oxaliplatin allergic reactions were most commonly characterized by skin and occurred at any time of the medication[21]. In intravenous chemotherapy, oxaliplatin has clearly demonstrated dose-limiting neurotoxicity. Neurotoxicity occurs in 15% of patients at a cumulative oxaliplatin dose of 750 $mg \cdot m^{-2}$ and 50% at 1170 $mg \cdot m^{-2}$[19]. Cumulative oxaliplatin dose was not significantly different between the two groups in our study [157.3 (80.3, 322.4) vs. 206.6 (139.1, 324.2), P=0.161]. Therefore, we speculated that the cumulative dose of oxaliplatin in oxaliplatin-based HAIC therapy would have a lesser impact on serious ADR (CTCAE ≥ 3).

Cancer development and treatment are associated with inflammation, and chronic inflammation promotes tumor progression and treatment resistance[22,23]. Conversely, acute inflammatory responses can stimulate various inflammatory factors, cytokines, and promote anti-tumor effects. Vascular endothelial cells play an important role in the inflammatory process by regulating vascular permeability and influencing inflammatory cell infiltration[24]. The known mechanism of oxaliplatin-associated hepatic sinusoidal obstruction syndrome is oxaliplatin-induced oxidative stress and inflammatory response in the liver, resulting in hepatic sinusoidal endothelial cell injury[21]. Whether oxaliplatin-based HAIC therapy then leads to endothelial cell injury or produces an acute inflammatory response in the hepatic arterial vasculature has not been reported. We found that the statistically significant increases in NEUT and IL-6 were more pronounced in the ADR group as compared to the no-ADR group. TBIL, ALT, AST, ALP, WBC, NEUT, PCT, CRP, TNF, IL-2R, IL-6, and IL-10 were significantly increased after HAIC treatment in the ADR group (P<0.05). We speculate that oxaliplatin-based HAIC therapy may produce a cytokine storm that affects NEUT, IL-6 is substantially elevated. While it suppresses tumors, it can also cause an acute inflammatory response that can lead to liver damage or even symptoms such as allergy and fever. Notably, the risk of serious ADR may be higher during the 3rd or subsequent HAIC treatment cycle.

There were several limitations in this study. First, this is a retrospective study that still needs to be evaluated by prospective studies with a larger sample size. Second, subgroup analysis was precluded by the small sample size. The effects of different HAIC treatments and the effects of combinations on ADR will continue to be studied by our research team.

5. Conclusions

Enhanced drug monitoring is required during oxaliplatin-based HAIC therapy to be on the alert for serious ADRs. Rash is usually the first symptom of an allergy, especially to oxaliplatin. An increase in inflammatory factors like NEUT and IL-6 may be the mechanism of serious ADRs (CTCAE ≥ 3).

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by Zhongshan Hospital (Xiamen), Fudan University Ethics Committee for Human Research.

Informed Consent Statement: The need for individual patient consent was waived by the Committee due to the retrospective nature of the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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Conflicts of Interest: The authors declare no conflicts of interest.

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