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Original Article

Effect of tigecycline on patients with pulmonary infection after acute leukemia chemotherapy and its effect on serum inflammatory factors and liver and kidney function

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Abstract: Objective: To explore the effect of tigecycline on patients with pulmonary infection with acute leukemia after chemotherapy (PIALC) and its effect on serum inflammatory factors and liver and kidney function. Methods: A total of 62 patients with PIALC were enrolled in our hospital. Patients were randomly divided into observation group (OG) and control group (CG) according to random number table, with 31 cases in each group. CG was treated with a conventional dose of tigecycline (50 mg, 1/12 h), and the observation group was treated with an overdose of tigecycline (100 mg, 1/12 h). The serum levels of IL-1β, IL-6, TNF-α and CRP were measured by double antibody sandwich enzyme-linked immunosorbent assay (ELISA). The total effective rate was evaluated according to the evaluation criteria of clinical efficacy, and the liver and kidney function tests of the two groups were observed. Results: The total effective rate of OG was 74.19%, and the total effective rate of CG was 54.84%. There was a statistical difference between the groups ($P < 0.001$). The serum levels of inflammatory cytokines tumor necrosis factor (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), and c-reactive protein (CRP) were decreased in both groups after treatment compared with those before treatment ($P < 0.001$). The level of inflammatory factors in OG was decreased more than that in CG ($P < 0.005$). There were differences in the levels of alanine aminotransferase (GPT/ALT) and aspartate aminotransferase (AST/GOT) before and after treatment in CG ($P < 0.05$). Conclusion: Tigacycline had little effect on liver and kidney function. Tigecycline was safe and effective in patients with PIALC.

Keywords: Tigecycline, acute leukemia, pulmonary infection, serum inflammatory factors, liver and kidney function

Introduction

Acute leukemia is a malignant proliferative disease of certain blood cells in the bone marrow hematopoietic system [1]. According to statistics, there were an estimated 350,000 leukemia cases in 2012 [2], and the incidence of acute myeloid leukemia in Calgary, Alberta, and Canada was 2.79 per 100,000 people [3]. At present, clinical treatment of leukemia, chemotherapy is an effective treatment program [4]. Acute leukemia destroys the body's normal immune response to infection, thereby weakening the body's ability to resist external pathogens, thus making patients susceptible to infection [5]. At the same time, patients receiving chemotherapy can cause bone marrow suppression, neutropenia and decreased immune function [6]. If left without clinical intervention, it will develop into respiratory failure, sepsis, multiple organ dysfunction syndrome, etc., and severe cases can also lead to death [7]. How to give drugs to patients with PIALC in clinical practice is worthy of our study.

Tigecycline is a new generation of broad-spectrum glycylcycline antibiotics [8, 9]. By binding to bacterial ribosome for 30S subunits, it inhibits bacterial protein synthesis and bacterial growth without tetracycline resistance [10]. It maintains good antibacterial activity against common pathogenic bacteria or multi-drug resistant bacteria [11], widely covering G+ coccus, G-bacillus, methicillin-resistant staphylococcus aureus (MRSA), stenotrophomonas maltophilia and multi-drug resistant acineto-

bacter baumannii. Tigecycline can effectively treat the pulmonary infection after adjuvant leukemia chemotherapy. Cuadros M et al. [12] elucidated the relationship between miR-155 and leukemia by studying the expression of miR-155 in leukemia cell lines. Brewer C J et al. [13] demonstrated the promotion of miR-126 on the development of inv (16) acute myeloid leukemia. Because the detection method of miRNA is complicated and cumbersome, this experiment will detect the levels of TNF-α [14], IL-1β [15], IL-6 [16], and CRP [17] in the serum of PIALC, in order to provide reference for clinical diagnosis and treatment.

At the same time, tigcycline is a new type of antibacterial drug with few clinical applications, but there is still a lack of extensive evaluation of its safety, the most common adverse drug reactions are nausea and vomiting [18]. There are also reports of liver dysfunction [19] and coagulopathy [20] after the use of tigecycline. For patients with pulmonary infection induced by the use of tigecycline in the treatment of acute leukemia chemotherapy, it is necessary to monitor whether the liver and kidney function is abnormal, so as to further study the safety of tigecycline.

The purpose of this study was to analyze the clinical efficacy, serum inflammatory factors and liver and kidney functions of acute leukemia after treatment with tigecycline in PIALC, so as to provide references for clinical treatment.

Materials and methods

General information

A total of 62 patients with pulmonary infection who were treated with acute leukemia after chemotherapy were enrolled in our hospital. Patients were divided into observation group (n = 31) and control group (n = 31) using random number table. CG was treated with a conventional dose of tigecycline (50 mg, 1/12 h), and OG was treated with an overdose of tigecycline (100 mg, 1/12 h). This study was approved by the Ethics Committee of No. 1 Hospital, Anhui Medical University. All the above subjects have signed informed consent.

Inclusion and exclusion criteria

Inclusion criteria: PIALC [21]; patients who were not treated with antibiotics 2 days before the study; patients who received treatment in our hospital; patients who were ineffective with carbapenems; with an age of 18-70 years; patients who can cooperate with the study; patients who have signed informed by patients or immediate family members; patients with complete medical records.

Exclusion criteria: Patients with important organ damage such as heart, liver, spleen, lung, kidney; patients with infections other than the lungs; patients with liver and kidney damage after chemotherapy; patients who died during the treatment; patients with mental illness and speech dysfunction; patients with pregnant and lactation; patients who have recently received steroid therapy.

Method

Treatment method: OG was treated with an intravenous drip of overdose of tigecycline (purchased from Jiangsu Haosen Pharma Co, Ltd, China). The first dose was 100 mg, then each dose was 100 mg, administered once every 12 hours. The average medication duration was 12.2 ± 3.1 d. CG was treated with a conventional dose of tigecycline, the first dose was 100 mg, and then each dose was 50 mg, administered once every 12 hours. The average medication duration was 13. 6 ± 2.9 d, and all patients were given anti-pyretic, antitussive, antiasthmatic, oxygen therapy and other supportive treatment.

Criteria for clinical efficacy: The evaluation criteria for clinical efficacy were as follows: (1) Cured: After taking the drug, the absorption rate of the patients' pulmonary inflammatory lesions exceeded 60% by chest CT examination, and the sputum culture results showed that the pathogens were completely cleared and the body temperature returned to normal; (2) Markedly effective: After taking the drug, the absorption rate of the patients' pulmonary inflammatory lesions exceeded 50% by chest CT examination, and the sputum culture results showed that the pathogens were completely cleared, and the body temperature decreased significantly. (3) Effective: The clinical symptoms of patients improved significantly after taking the drug, but the absorption of lung inflammatory lesions was not obvious; (4) Ineffective: After taking the drug, the patient's clinical symptoms and lung inflammation le-

Table 1. Comparison of clinical data [n (%)]

	Observation group (n = 31)	Control group (n = 31)	X^2 or t	*P*
Age	52.30 ± 2.44	53.10 ± 1.74	1.486	0.142
Gender			0.065	0.799
Male	15 (48.39)	16 (51.61)		
Female	16 (51.61)	15 (48.39)		
Weight (KG)	59.67 ± 7.64	60.31 ± 8.15	0.319	0.751
Course of disease (Week)	1.74 ± 1.04	1.72 ± 1.36	0.065	0.948
Marital status			0.081	0.776
Married	22 (70.97)	23 (74.19)		
Unmarried	9 (29.03)	8 (25.81)		
Nation			0.088	0.767
The Han Nationality	23 (74.19)	24 (77.42)		
Minority	8 (25.81)	7 (22.58)		
Place of residence			0.065	0.799
Town	17 (54.84)	16 (51.61)		
Rural	14 (45.16)	15 (48.39)		
Smoking			0.067	0.795
Yes	13 (41.94)	12 (38.71)		
No	18 (58.06)	19 (61.29)		
Alcohol			0.066	0.798
Yes	13 (41.94)	14 (45.16)		
No	18 (58.06)	17 (54.83)		
Motion			0.130	0.718
Yes	5 (16.13)	4 (12.90)		
No	26 (83.87)	27 (87.10)		

sions did not improve or even got worse. Total effective rate was calculated according to the evaluation criteria of clinical efficacy. Total effective rate = (number of cured cases + number of markedly effective cases + number of effective cases)/number of total cases × 100%.

ELISA: Blood samples were collected from patients before and after treatment. Blood samples were collected in the morning and sent to the laboratory for testing. Inflammatory indicators included IL-1β (BIOSS, bsk00026), IL-6 (Sino Biological Inc, KIT10395), TNF-α (Shanghai Xinfan Biotechnology Co., Ltd., XF16189Q), and CRP (Abbkine, ABB-KET6004-48T). The blood sample was added with 0.2 ml of 2% coagulant, centrifuged at 3000 rpm/min for 30 min, and stored at -20°C. ELISA was carried out in strict accordance with kit instructions.

Hepatic and renal function test: Blood samples were collected before and after treatment, and detected by automatic biochemical analyzer. Before and after treatment, the hepatic and renal function tests of the two groups were observed. Hepatic function indicators included alanine aminotransferase (GPT/ALT), aspartate aminotransferase (AST/GOT), total bilirubin (STB), direct bilirubin (CB), indirect bilirubin (UCB). Renal function indicators included urea nitrogen (BUN), uric acid (UA), creatinine (CR) and 24 h urine protein.

Statistical method: All experimental results were statistically calculated using SPSS 24.0 statistical software (Shanghai Yuchuang Network Technology Co., Ltd.). All graphics were drawn using Graphpad 8 software (Shenzhen Tianrui Software Technology Co., Ltd.) and the results were checked twice. The count data were expressed in terms of rate, and the chi-square test was used for comparison between groups. Measurement data were expressed in the form of mean ± standard deviation, and t-test was used for comparison between groups. $P < 0.050$ was considered statistically significant.

Results

Two groups showed no difference in baseline data

There was no difference in the age, gender, weight, course of disease, marital status, ethnicity, place of residence, smoking, drinking, and exercise in the clinical data of OG and CG ($P > 0.050$), which proved that the two groups of patients were comparable (**Table 1**).

No significant differences existed in two groups

The results showed that the total effective rate of OG was 74.19%, and that of CG was 54.84%. OG was superior to CG, and there was a statisti-

Table 2. Comparison of clinical therapeutic effect between two groups after treatment

Clinical efficacy	Observation group (n = 31)	Control group (n = 31)	X^2	*P*
Cure	23	10	10.95	< 0.001
Markedly effective	5	8	0.876	0.349
Effective	2	7	3.248	0.071
Invalid	1	6	4.026	0.045
Total effective	96.77	80.64	13.07	< 0.001

Table 3. Comparison of adverse reactions between two groups after treatment

Side effects	Observation group	Control group	X^2	*P*
Nausea and vomiting	3	4	0.161	0.688
Liver dysfunction	0	1		
Coagulation dysfunction	0	1		
Rash	1	0		
Incidence rate	12.9	19.35	1.339	0.247

cal difference between the groups (P < 0.001) (**Table 2**).

The most common adverse reactions in the treatment of patients in OG included 3 cases of nausea and vomiting, 1 case of mild skin rash, and the overall incidence of adverse reactions was 12.9%. In CG, there were 4 cases of adverse reactions of nausea and vomiting, 1 case of abnormal liver function and 1 case of coagulation dysfunction, and the total incidence of adverse reactions was 19.35%. There was no significant difference between the two groups (P < 0.05) (**Table 3**).

Observation group showed lower inflammatory factors levels

The TNF-α level in the observation group before treatment (42.37 ± 1.28) was significantly higher than that after treatment (13.37 ± 1.22). The TNF-α level in the control group before treatment (42.56 ± 1.73) was significantly higher than that after treatment (21.56 ± 1.38) (P < 0.05). TNF-α level in the observation group was significantly lower than that in the control group (P < 0.05, **Figure 1A**). The level of IL-1β in the observation group before treatment (46.68 ± 0.47) was significantly higher than that after treatment (22.49 ± 1.59). The level of IL-1β in the control group before treatment (46.32 ± 1.41) was significantly higher than that after treatment (29.63 ± 0.33) (P < 0.05). IL-1β level in the observation group was significantly lower than that in the control group (P < 0.05, **Figure 1B**). The level of IL-6 in the observation group before treatment (80.42 ± 1.38) was significantly higher than that after treatment (33.26 ± 1.47). The IL-6 level in the control group before treatment (80.91 ± 0.57) was significantly higher than that after treatment (43.27 ± 1.28). IL-6 level in the observation group was significantly lower than that in the control group (P < 0.05, **Figure 1C**). The level of CRP in the observation group before treatment (73.61 ± 1.63) was significantly higher than that after treatment (16.84 ± 2.74). The CRP level in the control group before treatment (73.94 ± 1.47) was significantly higher than that after treatment (30.75 ± 1.34). CRP level in the observation group was significantly lower than that in the control group (P < 0.05, **Figure 1D**).

No significant differences existed in hepatic and renal functions

There was no difference in the alanine aminotransferase (GPT/ALT), aspartate aminotransferase (AST/GOT), total bilirubin (STB), and direct bilirubin (CB) levels in OG before and after treatment (P > 0.05). There were differences in the levels of alanine aminotransferase (GPT/ALT) and aspartate aminotransferase (AST/GOT) before and after treatment in CG (P < 0.05). The total bilirubin, direct bilirubin and indirect bilirubin levels showed no differences (P > 0.05). There were no differences in the levels of urea nitrogen (BUN), uric acid (UA), creatinine (CR) and 24 h urine protein between the two groups before and after treatment (P > 0.05) (**Tables 4**, **5**).

Discussion

The most common adverse event in chemotherapy for acute leukemia patients is infection (25 of 29 patients [86%]) [22]. Compared with ordinary pulmonary infection, acute leukemia chemotherapy patients can be exposed to a larger number, more complex variety and a higher level of drug resistance. Moreover, patients with chemotherapy have a long hospital-stay, and the chance of exposure to pathogens

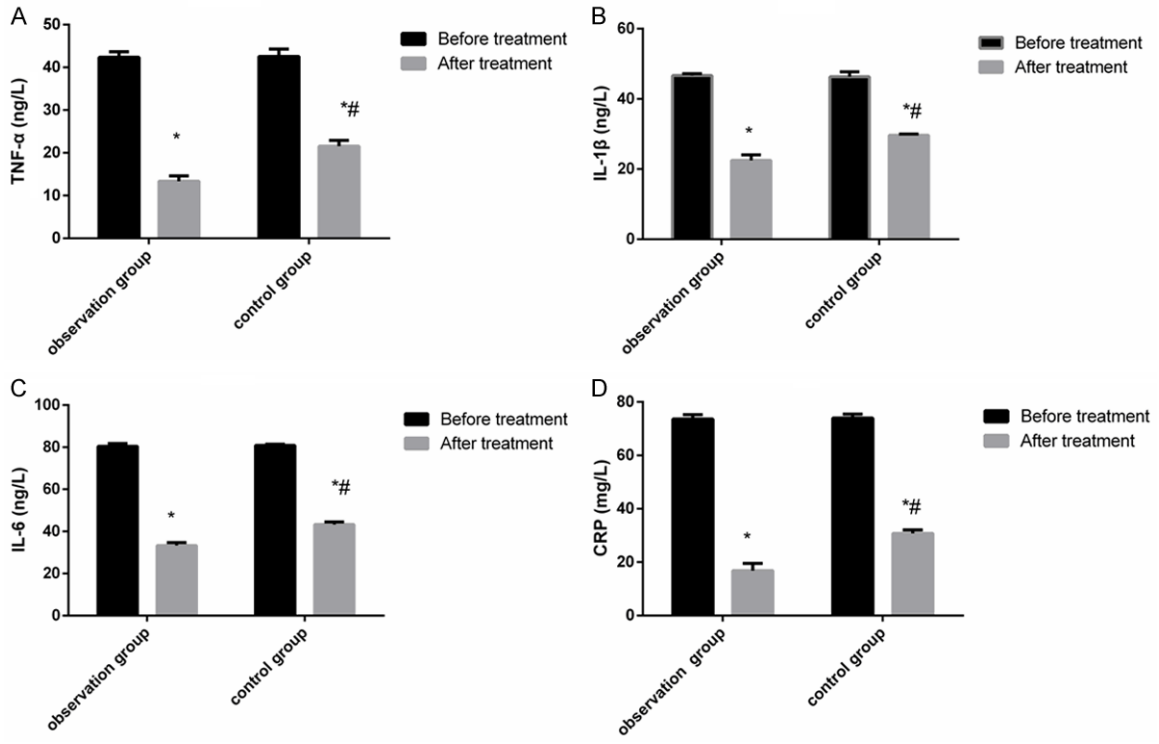

Figure 1. A. Content of TNF-α in serum of patients with PIALC. In OG and CG, the TNF-α content before treatment was higher than that after treatment; There was no significant difference in TNF-α levels between OG and CG before treatment. After treatment, the content of TNF-α in OG was higher than that in CG. *Indicated that the serum levels of TNF-α in patients with PIALC were compared with those before treatment ($P < 0.05$); #indicated that the serum levels of TNF-α in OG and CG were compared with those after treatment ($P < 0.05$). B. Content of IL-1β in serum of patients with PIALC. In OG and CG, the IL-1β content before treatment was higher than that after treatment; There was no significant difference in IL-1β levels between OG and CG before treatment. After treatment, the content of IL-1β in OG was higher than that in CG. *Indicated that the serum levels of IL-1β in patients with PIALC were compared with those before treatment ($P < 0.05$); #Indicated that the serum levels of IL-1β in OG and CG were compared with those after treatment ($P < 0.05$). C. Content of IL-6 in serum of patients with PIALC. In OG and CG, the IL-6 content before treatment was higher than that after treatment; There was no significant difference in IL-6 levels between OG and CG before treatment. After treatment, the content of IL-6 in OG was higher than that in CG. *Indicated that the serum levels of IL-6 in patients with PIALC were compared with those before treatment ($P < 0.05$); #indicated that the serum levels of IL-6 in OG and CG were compared with those after treatment ($P < 0.05$). D. Content of CRP in serum of patients with PIALC. In OG and CG, the CRP content before treatment was higher than that after treatment; There was no significant difference in CRP levels between OG and CG before treatment. After treatment, the content of CRP in OG was higher than that in CG. *Indicated that the serum levels of CRP in patients with PIALC were compared with those before treatment ($P < 0.05$); #indicated that the serum levels of CRP in OG and CG were compared with those after treatment ($P < 0.05$).

in the hospital is increased, which may lead to severe pulmonary infection [23]. Pneumonia is the leading cause of death during induction chemotherapy in acute leukemia [24], mainly due to long-term neutropenia. Given the high morbidity and mortality of pulmonary infection [25, 26], patients with acute leukemia require therapeutically effective interventions. At present, the number of multi-drug resistant pathogens is increasing [27], making treatment of infections challenging. Tigecycline is the first drug approved by the US Food and Drug Administration (FDA) for the severe infection caused by glycylcycline antibiotics and multidrug-resistant bacteria [28]. Currently, tigecycline has successfully treated patients with acute leukemia infection. Cases are reported in related literature [29]. This paper aims to evaluate the efficacy of tigecycline in PIALC and the effect on serum inflammatory factors and hepatic and renal function in patients.

Studies have shown that the total effective rate of CG was 54.84%, and the incidence of adverse reactions was 19.35%. The total effective rate of OG was 74.19%, the incidence of

Table 4. Comparison of liver function between the two groups before and after treatment

Index	Observation group		T	*P*	Control group		T	*P*
	Before	After			Before	After		
GPT/ALT (U/L)	28.31 ± 1.38	28.82 ± 1.27	1.514	0.135	28.21 ± 1.23	51.39 ± 1.43	68.42	< 0.001
AST/GOT (U/L)	30.48 ± 0.23	30.54 ± 0.64	0.491	0.62545	30.86 ± 1.39	49.43 ± 1.59	48.96	< 0.001
STB (μmol/L)	9.83 ± 0.34	9.77 ± 0.53	0.531	0.598	9.62 ± 0.22	9.71 ± 0.42	1.057	0.295
CB (μmol/L)	5.48 ± 1.49	5.71 ± 1.72	0.563	0.576	5.37 ± 1.37	5.60 ± 1.19	0.7057	0.483
UCB (μmol/L)	7.82 ± 1.43	7.71 ± 1.63	0.283	0.779	7.57 ± 1.33	7.31 ± 1.26	0.790	0.432

Table 5. Comparison of renal function between two groups before and after treatment

Index	Observation group		T	*P*	Control group		T	*P*
	Before	After			Before	After		
BUN (mmol/L)	4.92 ± 0.83	5.19 ± 0.23	1.745	0.086	4.87 ± 0.55	5.07 ± 0.26	1.830	0.072
UA (μmol/L)	374.39 ± 1.29	374.46 ± 1.38	0.206	0.837	373.78 ± 1.38	374.17 ± 0.98	1.283	0.204
Cr (μmmol/L)	83.98 ± 1.36	84.28 ± 1.47	0.834	0.407	83.39 ± 1.34	83.76 ± 1.07	1.201	0.234
24-hour urinary Protein Quantification (mg/24 h)	74.02 ± 1.28	73.81 ± 1.39	0.618	0.5338	73.93 ± 1.26	73.84 ± 1.01	0.757	0.310

adverse reactions was 12.9%, and the adverse reactions were mild. In both groups, serum TNF-α, IL-1β, IL-6 and CRP levels decreased after treatment ($P < 0.001$). The decrease of inflammatory factors in OG was more obvious than that in CG ($P < 0.005$). This suggests that overdose of tigecycline is more effective than conventional doses in PIALC, which is similar to the results of Bartoletti M et al. showing that tigacycline is superior to meropenem in reducing clostridium difficile infection after treatment of intraperitoneal infection [30]. After treatment, CG had a certain increase in GPT/ALT, AST/GOT content before treatment, and a case of adverse liver injury occurred. OG did not have serious adverse reactions, suggesting that the overdose of tigcycline is safer.

Tegacycline has an extended spectrum of antimicrobial activity and excellent tissue permeability, avoiding the effluent and target-mediated resistance to classical tetracycline obtained in the later stage, and is more excellent in drug resistance [31]. Lin et al. collected 37 children with acute lymphoblastic leukemia in the hospital's hematological malignancies [32], 18 of whom received maintenance doses. At the end of treatment, 48.7% of patients observed improvement, interleukin-10 levels were significantly reduced, and tooth discoloration was the only reported adverse event. However, there is a lack of prospective controlled studies to explicitly evaluate the efficacy and safety of tegacycline in children. Slawek D et al. analyzed 8 patients with severe infections of legionella using tigecycline antibacterial patients [33]. It was found that tigecycline was a potential second-line drug for the treatment of patients with severe infections of legionella who have poor response to conventional first-line drugs such as levofloxacin and azithromycin. The selected patients had multiple comorbidities and serious illnesses on admission. 7 of the 8 patients received combination therapy, and only one received tigecycline alone. It was difficult to determine whether it was due to the use of tegacycline or delayed response to the original protocol.

This study was designed to investigate the effect of tigecycline on PIALC and its effect on serum inflammatory factors and hepatic and renal function. This experiment is a prospective study with the advantage of being more objective and less susceptible to bias. It is the first study using tigecycline to treat PIALC, providing a basis for expanding its applicability and further monitoring the safety of tigecycline. However, due to the limited conditions of this experiment, there are still some shortcomings. The population is single, and the base of the research size is small. The relevant clinical trials conducted at this stage have certain limitations, which cannot fully elucidate the effect of tigecycline on PIALC, and its effects on serum inflammatory factors and hepatic and renal function. In the future, the efficacy and adverse reactions of tigecycline will be further explored, so as to provide more and more effective help for the treatment of pulmonary infection com-

plicated by acute leukemia chemotherapy in the future.

In summary, the use of tigecycline in the treatment of PIALC is effective, which is conducive to the improvement of infection, and has fewer adverse reactions and higher safety.

Disclosure of conflict of interest

None.

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