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Original Article

Clinical effect of teicoplanin on pulmonary infection after chemotherapy for hematologic malignancies

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Abstract: Objective: To explore the effects of teicoplanin on pulmonary infection after chemotherapy for hematologic malignancies. Methods: In the present retrospective study, 64 patients with pulmonary infection, who underwent chemotherapy for hematologic malignancies at Anhui No.2 Provincial People's Hospital from September 2019 to September 2021, were selected as an infection group, and their clinical data were retrospectively analyzed. Meanwhile, 30 patients without pulmonary infection after chemotherapy for hematologic malignancies were selected as a reference group. Patients in the infection group were subdivided into control and treatment groups (n=32 each) according to the different therapeutic regimens. The control group was given routine treatment with norvancomycin, while the treatment group was given teicoplanin combined with norvancomycin. The therapeutic effects, bacterial clearance rate, recovery time, clinical pulmonary infection score (CPIS), inflammatory factors and adverse reactions were compared between the two groups. The risk factors of pulmonary infection after treatment for hematologic malignancies were analyzed. Results: The treatment group exhibited higher total therapeutic effect and higher bacterial clearance rate than the control group ($P < 0.05$). The treatment group had shorter time to the recovery of white blood cell (WBC) count, time to the disappearance of cough and sputum, time to return to normal body temperature, and length of stay than the control group ($P < 0.05$). One month post-treatment, the levels of C-reactive protein, tumor necrosis factor-α, interleukin-1β, and procalcitonin in the treatment group were lower than those in the control group ($P < 0.05$). The CPISs at 7, 14, and 30 days after treatment were lower in the treatment group than those in the control group ($P < 0.05$). Compared with the reference group, the infection group had higher rate of diabetes, higher rate of glucocorticoid use, longer time of agranulocytosis, longer hospital stay and lower WBC count ($P < 0.05$). Multivariate Logistic regression analysis showed that agranulocytosis time, diabetes mellitus and glucocorticoid use were independent risk factors for pulmonary infection after treatment for hematologic malignancies ($P < 0.05$), and that higher WBC was a protective factor ($P < 0.05$). Conclusion: Teicoplanin in the treatment of pulmonary infection after chemotherapy for hematologic malignancies can improve the therapeutic effects, effectively clear bacteria, shorten the recovery time and reduce the inflammatory response.

Keywords: Teicoplanin, pulmonary infection, chemotherapy, hematologic malignancies, therapeutic effect

Introduction

Hematologic malignancies are considered to be one of the most common cancers and refer to diseases caused by abnormalities in the hematopoietic system. Hematologic malignancies, including myelodysplastic syndrome (MDS), multiple myeloma, lymphoma and leukemia, are characterized by anemia, fever, bleeding and granulocytopenia. Chemotherapy can be complicated by neutropenia. These patients are susceptible to infection owing to dysbiosis, gastrointestinal mucosal damage and low immune function. It should be noted that the lung is a high-risk site for infection, which not only affects treatment but also increases mortality [1-3]. In patients with hematologic malignancies, if the lung infection is not treated promptly and effectively after chemotherapy, the infection can cause respiratory failure, severe pneumonia and infectious shock, leading to high mortality [4-6]. Although drug regimens are employed to control infection in patients with such diseases, a unified treatment strategy is lacking. Teicoplanin is a glycopeptide antibiotic produced by *Actinomycetes*, which can easily penetrate human tissues and cells, and has the characteristics of long half-

life, high lipophilicity and few adverse reactions (such as nephrotoxicity). Teicoplanin can inhibit the synthesis of bacterial cell walls, thereby exerting bacteriostatic and bactericidal activities [7, 8]. Teicoplanin exhibits good efficacy against gram-positive bacteria such as *Streptococcus*, *Staphylococcus aureus* and anaerobic bacteria, suggesting that teicoplanin may provide a new treatment strategy for pulmonary infection after chemotherapy for hematologic malignancies. However, few reports have examined the clinical application of teicoplanin for the treatment of patients with hematologic malignancies. Therefore, in the present study, we explored the therapeutic effects of teicoplanin in the treatment of pulmonary infections after chemotherapy for hematologic malignancies.

Materials and methods

General data

In the present retrospective study, 64 patients with pulmonary infection after chemotherapy for hematologic malignancies admitted to Anhui No. 2 Provincial People's Hospital between September 2019 and September 2021 were selected as an infection group, and their clinical data were retrospectively analyzed. The patients were subdivided into a control group (n=32) and a treatment group (n=32) according to the distinct therapeutic regimens. The inclusion criteria were as follows: (1) patients who met the diagnostic criteria for leukemia, multiple myeloma and lymphoma in the Guide to Internal Diseases: Diseases of the Hematologic System [9]; (2) patients who underwent chemotherapy; (3) patients who met the diagnostic criteria for pulmonary infection after chemotherapy for hematologic malignancies [10]; (4) patients who were aged over 18 years; (5) patients who signed informed consent at the beginning of diagnosis and allowed the use of clinical data in further research; (6) patients with complete imaging examinations and medical records. Exclusion criteria were as follows: (1) patients who were allergic to the study drugs; (2) patients with psychiatric diseases, malignant tumors, or cardiac, hepatic or renal insufficiency; (3) patients with other infectious diseases; (4) patients with expected survival of < 3 months. Meanwhile, 30 patients without pulmonary infection after receiving chemotherapy for hematologic malignancies were selected as a reference group, and the medical records were retrospectively analyzed. The study was approved by the Medical Ethics Committee of Anhui No.2 Provincial People's Hospital.

Methods

In the control group, patients were given routine treatment with norvancomycin (North China Pharmaceutical Co., Ltd.; H20057443; specifications: 0.8 g). A dose of 400 mg norvancomycin was added to 200 mL of normal saline (Huaren Pharmaceutical Co., Ltd.; H20093777; specification: 2000 mL:18 g) for intravenous drip once every 8 h for 4 weeks. Other treatments included maintenance of water-electrolyte balance, nutritional support, expectorant treatment, analgesics, tracheal dilators and oxygenation, as well as active treatment of underlying diseases.

Patients in the treatment group were given norvancomycin combined with teicoplanin (Zhejiang Medicine Co., Ltd.; H20040387; specification: 0.2 g). A dose of 400 mg norvancomycin was added to 200 mL of normal saline for intravenous drip once every 8 h for 4 weeks. Additionally, a dose of 400 mg of teicoplanin was added to 250 mL of normal saline for intravenous drip, and the drip was administered within 0.5-1 h, once a day for 4 weeks.

Observation indicators

Response rate: The response rate was evaluated one month post-treatment according to the guidelines for the clinical application of antimicrobial drugs. Cure: all pathogenic bacteria were cleared, and symptoms and signs disappeared; markedly effective: most pathogenic bacteria were cleared, and symptoms and signs improved significantly; effective: pathogenic bacteria were partial cleared, and symptoms and signs improved; ineffective: failure to meet the above criteria. The total response rate = (cured cases + markedly effective cases + effective cases)/total cases × 100%.

Bacterial clearance rate: Sputum specimens were collected from patients one month post-treatment, and a VIET32 automatic bacterial identification instrument (bioMérieux, France) was used to culture and identify bacteria and

evaluate the bacterial clearance. Specimens free of pathogenic bacteria were considered completely cleared; specimens with only some pathogenic bacteria were considered partially cleared; specimens with no change in bacteria comparing to the original were considered not cleared. Total clearance rate = (completely cleared cases + partially cleared cases)/total cases × 100%.

Adverse reactions

The incidences of adverse reactions, including nausea and vomiting, liver function damage, rash, headache and thrombocytopenia, were recorded.

Recovery time

The time to the recovery of white blood cell (WBC) count, time to the disappearance of cough and sputum, time to return to normal body temperature and length of stay were recorded.

Inflammatory factors

Fasting venous blood (5 mL) was collected from patients by the nurses one day before and one month after treatment. The supernatant was centrifuged at 3500 rpm for 10 min and stored at -20°C until further use. Serum levels of tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) were determined using enzyme-linked immunosorbent assays. Serum levels of C-reactive protein (CRP) were measured using an immunoturbidimetric assay, and serum levels of procalcitonin (PCT) were measured using an enzyme-linked fluorometric assay. The relevant kits were provided by Nanjing Sempega Biotechnology Co., and tests were performed in strict accordance with the manufacturer's instructions.

Pulmonary infection score

The severity of pulmonary infection was assessed by the nurses one day before and one month after treatment according to the clinical pulmonary infection score (CPIS), which consists of six items, namely tracheal aspirate culture or sputum culture, gas exchange index, volume and shape of secretions, WBC count, 12-h average body temperature, and infiltrative shadow on chest film, with a score of 0-2 points for each item, totaling 12 points. The score was proportional to the severity of the pulmonary infection.

Analysis of risk factors

The risk factors of pulmonary infection after treatment of hematologic malignancies were analyzed.

Statistical analysis

Data were analyzed using SPSS 19.0 (IBM Corp., Armonk, NY, USA). The measurement data (conforming to normal distribution) were described as mean ± standard deviation (mean ± SD). The independent sample t-test was used for inter-group comparison, and the paired sample t-test was used for intra-group comparison. Counting data were described as n (%) and examined using χ^2 tests. Multivariate analysis was performed using multivariate logistic regression analysis. $P < 0.05$ was considered statistically significant.

Results

General data

No statistically significant differences were observed in proportion of male to female, mean age, and type of blood disorders between the treatment and control groups ($P > 0.05$) (**Table 1**).

Response rate

The total response rate in the treatment group (93.75%) was higher than that in the control group (65.63%) ($P < 0.05$) (**Table 2**).

Bacterial clearance rate

The bacterial clearance rate in the treatment group (93.75%) was higher than that in the control group (62.50%) ($P < 0.05$) (**Table 3**).

Recovery time

The time to the recovery of WBC count, time to the disappearance of cough and sputum, time to return to normal body temperature and length of stay in the treatment group were shorter than those in the control group ($P < 0.05$) (**Figure 1**).

Table 1. Comparison of general information [n (%)]/($\bar{x}$±s)

Clinical data		Control group (n=32)	Treatment group (n=32)	t/χ^2	*P*
Sex	Male	18 (56.25)	17 (53.13)	0.063	0.801
	Female	14 (43.75)	15 (46.87)		
Age (years)		55.29±4.68	55.35±4.71	0.051	0.959
Type of hematologic disease	MDS	8 (25.00)	10 (31.25)	0.072	0.642
	Lymphoma	7 (21.87)	8 (25.00)		
	Multiple myeloma	5 (15.63)	3 (9.38)		
	Leukemia	12 (37.50)	11 (34.37)		

MDS: myelodysplastic syndrome.

Table 2. Comparison of treatment response rate between the two groups [n (%)]

Group	Number of cases	Cure	Markedly effective	Effective	Ineffective	Total response rate
Control group	32	2 (6.25)	8 (25.00)	11 (34.37)	11 (34.36)	21 (65.62)
Treatment group	32	5 (15.63)	15 (46.87)	10 (31.25)	2 (6.25)	30 (93.75)
χ^2	-	-	-	-	-	7.819
P	-	-	-	-	-	0.005

Table 3. Comparison of bacterial clearance rates between the two groups [n (%)]

Group	Number of cases	Completely cleared	Partially cleared	Not cleared	Clearance rate
Control group	32	7 (21.87)	13 (40.63)	12 (37.50)	20 (62.50)
Treatment group	32	11 (34.38)	19 (59.37)	2 (6.25)	30 (93.75)
χ^2	-	-	-	-	9.142
P	-	-	-	-	0.002

Inflammatory factors

No statistically significant differences were noted in levels of CRP, TNF-α, IL-1β and PCT between the two groups one day before treatment ($P > 0.05$). One month after treatment, the levels of CRP, TNF-α, IL-1β and PCT were lower than those before treatment in both groups, and were lower in the treatment group than those in the control group ($P < 0.05$) (**Figure 2**).

Pulmonary infection score

No statistically significant differences were found in the CPISs between the two groups one day before treatment ($P > 0.05$). The CPISs at 7, 14 and 30 days after treatment were lower in the treatment group than those in the control group ($P < 0.05$). In both groups, the CPISs at 14 and 30 days after treatment were lower than those at 7 days after treatment ($P < 0.05$), and the CPISs at 30 days after treatment were lower than those at 14 days after treatment ($P < 0.05$) (**Figure 3**).

Adverse reactions

The incidence of adverse reactions was slightly lower in the treatment group (9.37%) than that in the control group (28.12%), but the difference was not statistically significant ($P > 0.05$) (**Table 4**).

Univariate analysis

Compared with the reference group, the infection group had higher rates of diabetes and glucocorticoid use, longer time of agranulocytosis, longer hospital stay and lower WBC level ($P < 0.05$) (**Table 5**).

Multivariate Logistic regression analysis

Multivariate Logistic regression analysis showed that agranulocytosis time, diabetes mellitus and glucocorticoid use were independent risk factors for pulmonary infection after treatment of hematologic malignancies ($P < 0.05$), and higher WBC was a protective factor ($P < 0.05$) (**Table 6**).

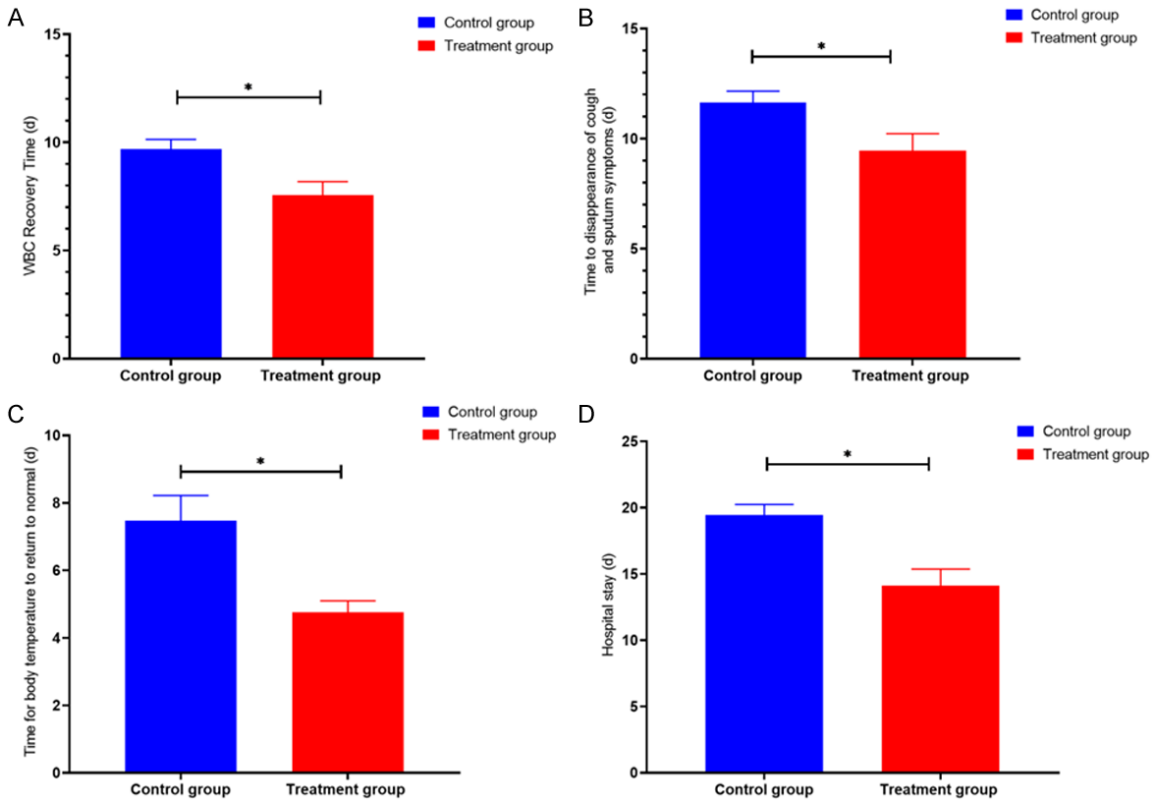

Figure 1. Recovery. Compared with the control group, the time of the recovery to white blood cell (WBC) count (A), the time to disappearance of cough and sputum (B), the time to the return of normal body temperature (C), and the length of stay (D) were shorter in the treatment group ($P < 0.05$), $^{*}P < 0.05$.

Discussion

Typically, hematological malignancies include leukemia, lymphoma, multiple myeloma and MDS, which are more complex, severe and more rapidly progressive than other diseases, and require prompt and effective treatment. Chemotherapy is often employed for hematologic malignancies and can rapidly improve patient symptoms. However, chemotherapy tends to cause agranulocytosis during the myelosuppressive phase, leading to infections. Among these, gram-negative bacterial infections are the most common, followed by gram-positive bacterial infections, which can lead to infectious shock and respiratory failure in severe cases due to bacteremia, thus increasing mortality [11]. Neutrophils are important defense cells, and infections in neutropenic patients with hematologic malignancies are characterized by severe conditions, rapid progression and high mortality. Given the presence of varying degrees of immune dysfunction in neutropenic patients, the requirement for repeated chemotherapy for hematologic malignancies and the widespread clinical use of peripherally inserted central catheter placement and deep vein placement, infections in patients with hematologic malignancies frequently necessitate comprehensive coverage with broad-spectrum antibacterial drugs, which increases the risk of pulmonary infections [12]. The widespread clinical application of quinolones and third-generation cephalosporins has led to the increase of drug-resistant strains of gram-positive cocci, and methicillin-resistant *S. aureus* is considered to be one of the most important pathogens inducing nosocomial infections [13]. Leukemia reportedly accounts for 53.2% of the disease distribution in patients with pulmonary infections after chemotherapy for hematologic malignancies. Owing to impaired leukocyte differentiation, leukemic patients may have a large number of clonal growths of primitive cell, loss of bacterial phagocytosis and inhibition of normal leukocyte production, thereby increasing the risk of infection [14, 15]. It has been reported that

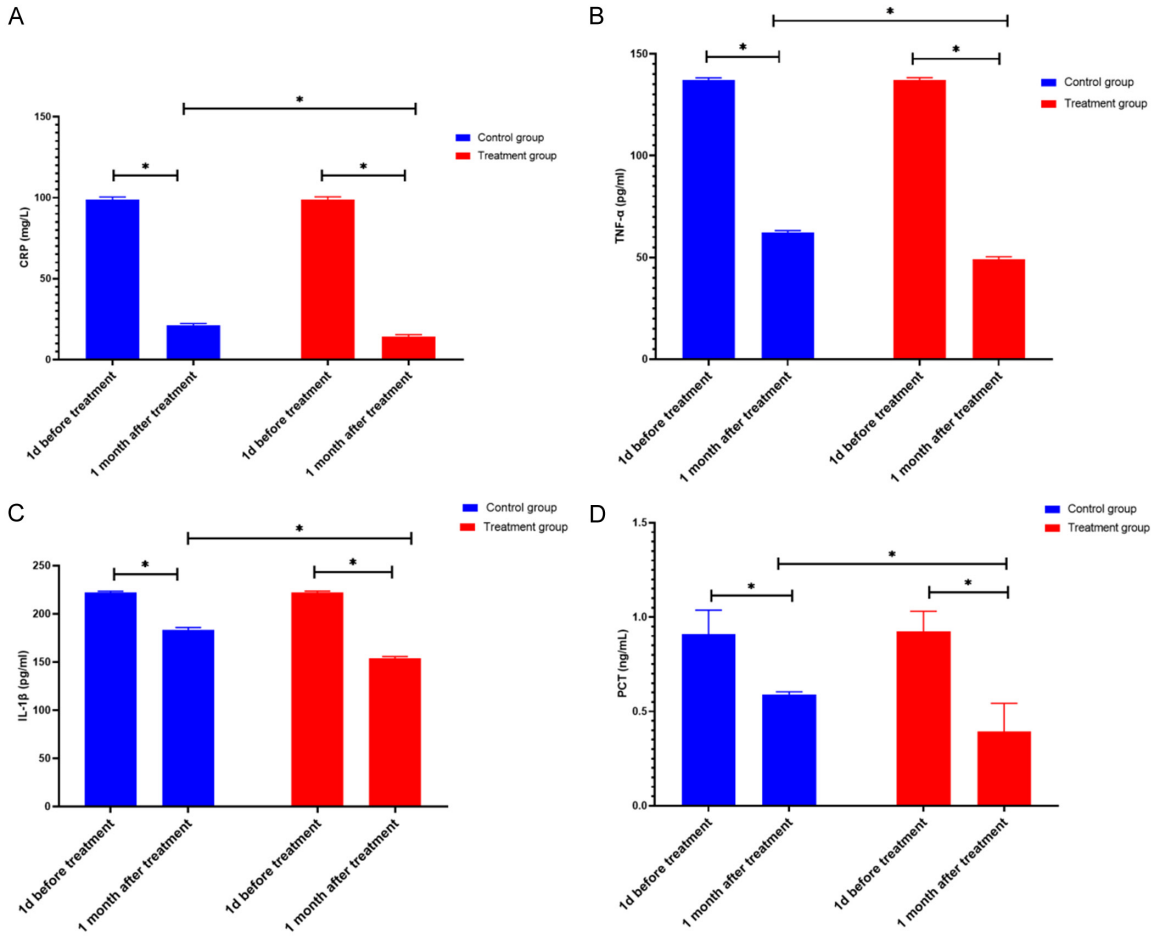

Figure 2. Comparison of inflammatory factors. (A) C-reactive protein (CRP), (B) Tumor necrosis factor-α (TNF-α), (C) Interleukin-1β (IL-1β), (D) Procalcitonin (PCT). $^{*}P < 0.05$.

hyperthermia is the main symptom of pulmonary infections in patients with hematologic malignancies after chemotherapy, accounting for 96.6%, and involving the respiratory system; 27.2% of patients had unclear foci of infection, and 24.1% had sepsis. These findings suggests that fever is often the only manifestation of infection in patients with hematologic malignancies, while the remaining signs and symptoms appear subtle [16]. Patients with neutropenia and hyperthermia should be monitored to prevent severe infections or sepsis. Multiple blood cultures and imaging examinations are needed to improve serologic examinations of infection, and anti-infective treatment should be actively administered to improve the prognosis of patients.

As for the risk factors of pulmonary infection after chemotherapy for hematologic malignancies, this study showed that compared with the reference group, the infection group had higher rates of diabetes and glucocorticoid use, longer time of agranulocytosis, longer hospital stay and lower WBC count. Multivariate Logistic regression analysis showed that agranulocytosis time, diabetes mellitus and glucocorticoid use were independent risk factors for pulmonary infection after treatment of hematologic malignancies, and higher WBC was a protective factor. This suggests that pulmonary infection is more likely to occur after chemotherapy for hematologic malignancies, and the risk factors include long duration of agranulocytosis, diabetes mellitus and glucocorticoid use. The reason may be that pulmonary infection after chemotherapy in patients with hematologic malignancies is closely related to the decline of autoimmune function and the use of corticosteroids. Patients with diabetes mellitus and long-term

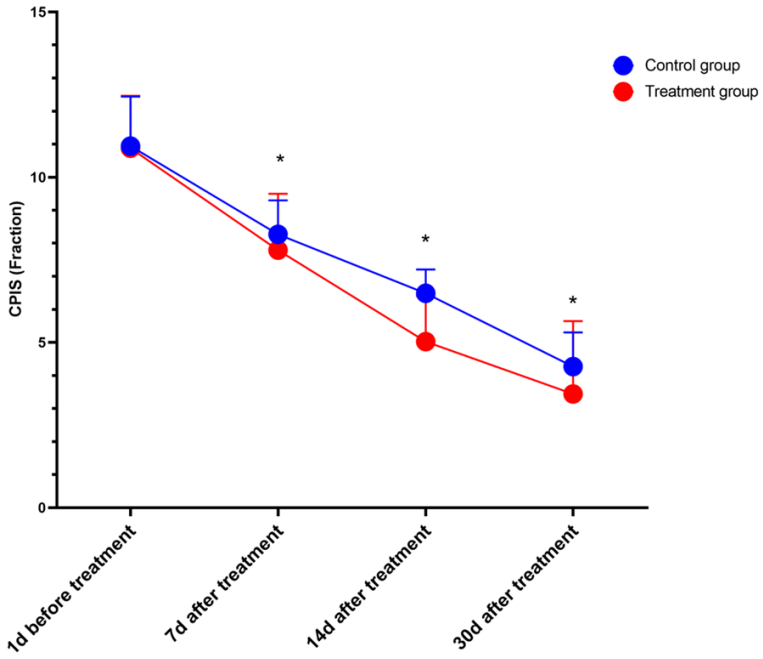

Figure 3. CPIS. CPIS: clinical pulmonary infection score. *$P < 0.05$.

hyperglycemia can have immune dysfunction, reduced activation of T lymphocytes and macrophages, and weakened defense against pathogenic bacteria, which can promote the increase of plasma osmotic pressure, increase of blood viscosity and decrease of blood flow speed, creating favorable conditions for the propagation of pathogenic bacteria and infection. Cellular immunity is extremely important for the prevention of lung infection, especially neutrophil phagocytosis. Granulocytosis can lead to insufficient immunity and increase the risk of lung infection. Data have shown that hematologic malignancies and chemotherapy can lead to the decrease of WBC count and function, and then increase the risk of lung infection [17]. It is necessary to actively carry out therapy for WBC elevation, strengthen nutritional support and prevent the occurrence of infection in patients with leukocyte segregation. Glucocorticoids play an important role in the treatment of hematologic malignancies, and it can also adversely affect the body's immunity, inhibit neutrophil function and increase the risk of infection.

In recent years, teicoplanin has been used in clinical treatment for patients with pulmonary infections after chemotherapy for hematologic malignancies. However, limited studies have examined this strategy. In the present study, the treatment group received additional teicoplanin, and our results revealed that the total response rate of the treatment group (93.75%) was higher than that of the control group (65.63%); the bacterial clearance rate of the treatment group (93.75%) was higher than that of the control group (62.50%); the time to the recovery of WBC count, the time to disappearance time of cough and sputum, the time to the return of normal body temperature and the length of stay in the treatment group were shorter than those in the control group; the CPISs at 7, 14, and 30 days after treatment were lower in the treatment group than those in the control group, suggesting that the application of teicoplanin in the treatment of pulmonary infections after chemotherapy for hematologic malignancies can rapidly improve symptoms, increase bacterial clearance, promote therapeutic effect and shorten the recovery time of patients. Teicoplanin is a new type of glycopeptide antibiotic with similar antibacterial activity and spectrum to vancomycin, but teicoplanin exerts potent antibacterial effects with few adverse reactions, and it is mainly used against gram-positive bacteria such as streptococci and staphylococci, and most anaerobic-positive bacterial infections, with good curative effects [18]. Teicoplanin for pulmonary infections after chemotherapy for hematologic malignancies can inhibit the synthesis of the new part of peptidoglycan, interfere with or damage the process of cell wall integration and firmness, and induce cell growth arrest, thereby resulting in cell death [19]. Moreover, teicoplanin is a time-dependent antimicrobial drug, mainly excreted in its original form via the kidneys, and requires loading dose administration to rapidly reach stable blood concentrations, owing to a protein binding rate of up to 95% and a half-life of up to 100 h [20]. However, in the present study, the therapeutic effect of different teicoplanin doses for patients with pulmonary infections after chemotherapy for hemato-

Table 4. Comparison of adverse reactions [n (%)]

Group	Number of cases	Nausea and vomiting	Liver function impairment	Skin rash	Headache	Thrombocytopenia	Incidence
Control group	32	3 (9.37)	1 (3.12)	2 (6.25)	2 (6.25)	1 (3.13)	9 (28.12)
Treatment group	32	1 (3.12)	0 (0.00)	1 (3.13)	1 (3.12)	0 (0.00)	3 (9.37)
χ^2	-	-	-	-	-	-	3.692
P	-	-	-	-	-	-	0.054

Table 5. Comparison of general data between the reference and infection groups

General data		Reference group (n=30)	Infection group (n=64)	χ^2/t	*P*
Sex	Male	16	33	0.138	0.710
	Female	14	31		
Age (years)		52.58±2.47	53.28±2.08	1.431	0.155
Underlying diseases	Hypertension	6	17	0.476	0.490
	Diabetes	3	21	5.590	0.018
	Hyperlipidaemia	6	11	0.109	0.741
	Heart and lung disease	10	25	0.286	0.592
	Renal function damage	5	14	0.343	0.557
WBC ($\times 10^9$/L)	≥ 1	19	49	1.786	0.181
	< 1	11	15		
Time of agranulocytosis (d)		10.35±2.24	12.79±3.01	3.952	0.000
Immunosuppressive agent use		3	8	0.123	0.725
Glucocorticoid use		12	47	9.771	0.001
Hospital stay (d)		27.66±5.26	31.72±5.47	3.395	0.001
PLT ($\times 10^9$/L)	≥ 100	18	36	0.117	0.731
	< 100	12	28		

WBC: white blood cells; PLT: platelets.

Table 6. Multivariate Logistic regression analysis

Influencing factor	β	SE	Wald	OR	95% CI	*P*
Diabetes	0.925	0.407	5.033	2.452	1.122-5.521	0.027
WBC	-0.204	0.086	5.877	0.812	0.691-0.964	0.018
Time of agranulocytosis	0.277	0.092	6.312	1.305	1.092-1.572	0.024
Glucocorticoid use	0.582	0.277	4.349	1.789	1.036-3.095	0.011
Hospital stay	0.144	0.089	2.532	1.154	0.966-1.381	0.157

WBC: white blood cells; SE: standard error; OR: odd ratio; 95% CI: 95% confidence interval.

logic malignancies was not examined, which will be further explored in future studies. Herein, the incidence of adverse reactions in the treatment group was slightly lower than that in the control group, but the difference was not statistically significant, suggesting that a series of adverse reactions may occur with teicoplanin for clinical treatment. In a study assessing 82 patients with pulmonary infection after chemotherapy for hematologic malignancies, teicoplanin was found to reduce adverse reactions from 31.59% to 11.07%, indicating a statistically significant difference when comparing with only vancomycin in terms of adverse reactions [21], which is inconsistent with the results of the present study. This may be related to the small sample size of the present study. Increasing the sample size in future studies could help clarify the safety of teicoplanin in the treatment of pulmonary infection after chemotherapy for hematologic malignancies. Inflammatory cytokines can accurately reflect

immune function, and inflammatory mediators are important indicators for the clinical evaluation of pulmonary infections [22, 23]. TNF-α is a pro-inflammatory cytokine synthesized and secreted by activated macrophages, which can promote an anti-interference effect by improving the phagocytosis of neutrophils. PCT is a crucial indicator for the clinical diagnosis and monitoring of bacterial infections, which can reflect the occurrence and active degree of the inflammatory response. IL-1β can stimulate the immune response, aggravate the inflammatory response and exert a wide range of immunomodulatory effects. CRP is a common clinical inflammatory marker that accurately reflects the degree of infection [24]. All above-discussed indicators are abnormally secreted in patients with pulmonary infections, mainly manifested as the downregulated expression of anti-inflammatory response factors and upregulated expression of pro-inflammatory response factors [25]. In the present study, it was found that CRP, TNF-α, IL-1β and PCT levels in the treatment group were lower than those in the control group one month after treatment, suggesting teicoplanin could downregulate CRP, TNF-α, IL-1β and PCT expressions and reduce the inflammatory response of the body. This effect may be related to the bactericidal, anti-inflammatory, and anti-infective effects of teicoplanin [26].

The present study was a single-center retrospective study with certain limitations. There was no statistically significant difference in complications, which may be related to the insufficient sample size. Therefore, high-quality multicenter randomized controlled trials with a larger sample size and long-term follow-up are needed to further explore the efficacy and safety of teicoplanin in the treatment of pulmonary infections after chemotherapy for hematologic malignancies.

In conclusion, the application of teicoplanin in the treatment of patients with pulmonary infection after chemotherapy for hematologic malignancies can effectively clear bacteria, improve therapeutic effects and reduce the inflammatory response. Pulmonary infection is easy to occur after chemotherapy for hematological malignancies. Positive identification of related risk factors and application of antibiotics to high-risk patients are conducive to reducing the risk of infection.

Disclosure of conflict of interest

None.

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