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Original Article

Comparison of clinical efficacy between chrono-chemotherapy and conventional chemotherapy in patients with non-small cell lung cancer

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Abstract: This work focused on the clinical efficacy of chrono-chemotherapy and conventional chemotherapy on patients with non-small cell lung cancer (NSCLC), providing a theoretical basis for the clinical promotion of chrono-chemotherapy. 60 NSCLS patients in our hospital were randomly enrolled into a chrono-chemotherapy group and a conventional chemotherapy group, with 30 cases in each. Patients were treated with the standardized first-line treatment TP regimen (paclitaxel + cisplatin). After two cycles of chemotherapy, the clinical efficacy and adverse reactions of patients receiving various methods were observed. After the chemotherapy, CD3+, CD4+, and CD28+ increased while NK cells, B cells, and CD28- decreased in the conventional chemotherapy group ($P<0.05$); CD3+, CD4+, CD4+CD8+, B cells, and CD28+ increased while CD8+, NK cells, and CD28- decreased in chrono-chemotherapy group ($P<0.05$). The progression-free survival (PFS) of patients in the chrono-chemotherapy group (3.29 ± 0.46 years vs 2.56 ± 0.35 years) was longer ($P<0.05$). The quality of life (QOL) score in the chrono-chemotherapy group was higher (64.83 ± 1.54 points vs 51.72 ± 1.89 points) ($P<0.05$). The incidences of leukopenia (63.33%) and nausea and vomiting (53.33%) in the conventional chemotherapy group were higher than those in the chrono-chemotherapy group (30.00% and 30.00, respectively) ($P<0.05$). The chrono-chemotherapy could improve the cellular immune function of NSCLS patients, prolong their survival period, elevate the QOL, and reduce the side effects.

Keywords: Chrono-chemotherapy, chrono-pharmacology, non-small cell lung cancer, cellular immunity, clinical efficacy

Introduction

Lung cancer is a common malignant tumor and has gradually become the leading cause of caner-induced death in China, especial the urban areas [1-3]. At present, the number of non-small cell lung cancer (NSCLC) patients is about 85% of all patients with various types of lung cancers [4, 5].

At present, the first-line treatment drugs for NSCLC clinical chemotherapy are mainly platinum, combined with paclitaxel and gemcitabine. According to data, the effective rate of treatment is 25%-35%, and the one-year survival rate is above 30% [6-8]. In recent years, compared with conventional chemotherapy, the popularization and application of chrono-chemotherapy has reduced chemotherapy toxicity, improved clinical efficacy, and greatly improved the quality of life of patients. Chrono-pharmacology is to explore the time-related physiological and pathological responses of the body to drugs, including pharmacological effects, adverse events, and pharmacokinetics [9, 10]. It aims to explore the periodic probability of biological individuals, estimate and determine the optimal administration time of different drugs, and provide a basis for clinical treatment to achieve high-efficiency and low-toxic drug therapy [11-13]. Clinical studies have shown that anticancer drugs reach different

peaks at different time points, and drug toxicity is also different. Chrono-chemotherapy is to use the principle of time to give chemotherapy drugs to tumor patients, so as to achieve the purpose of reducing drug toxicity and increasing the anti-tumor effect of drugs.

Various physiological states, biochemical functions, treatment mechanisms, and adverse reactions of the body all undergo rhythmic changes over time, resulting in chrono-pharmacology and chrono-therapeutics [14, 15]. Therefore, using the relevant theoretical knowledge of pharmacokinetics to formulate a reasonable dosing regimen can not only improve the clinical efficacy of the drug, but also reduce the adverse reactions of the prognosis. This work explored the clinical efficacy of chronotherapy on patients to offer a theoretical basis for the promotion and application of chronotherapy.

Materials and methods

Research objects

60 NSCLS patients confirmed by pathology or cytology in our hospital from October 2019 to October 2021 were randomly grouped into a chrono-chemotherapy group and a conventional chemotherapy group. 32 males and 28 females were included. The mean age was (45.37 ± 9.43) years old. The data of patients arranged in different groups were not statistically obvious and were comparable ($P>0.05$). This experiment was approved by the Medical Ethics Committee of Shengzhou People's Hospital, and the patients and their families were informed with in advance.

The criteria based on which the patients were included were as follows: patients with normal liver and kidney function, electrocardiogram, blood analysis, etc.; patients with no radiotherapy and chemotherapy within 30 days before the experiment; patients with expected survival period ≥6 months; and patients with Karnofsky (KPS) functional status score [16] greater than 70 points.

The exclusion criteria were set as follows: those with age <18 years old; patients with infectious diseases and mental diseases; and patients who received radiotherapy and chemotherapy or immunomodulatory treatment before the experiment.

Treatment methods

Patients in both the conventional chemotherapy group and the chrono-chemotherapy group were treated with the TP regimen (paclitaxel + cisplatin) as the standard first-line treatment for non-small cell carcinoma.

Patients in the conventional chemotherapy group were given with conventional chemotherapy. Paclitaxel 175 mg/m^2 (Jiangsu taxus pharmaceutical co., LTD., approved by H20067344) was administered and added to 500 mL of 5% glucose for intravenous drip. Cisplatin 30 mg/(m^2·d) (Hansoh Pharma, Jiangsu, China, approved by H20010743) was added to 500 mL of 0.9% normal saline for intravenous drip. The infusion time was scheduled at 9:00 every morning, with a normal drip rate.

The patients in chrono-chemotherapy group were given with chrono-chemotherapy. The deep vein catheterization and ZZB-150 automatic drug injection pump (Apon, Jiangsu, China) were adopted for drug infusion. Referring to the international research on chrono-chemotherapy of tumors, the TP program chrono-chemotherapy was carried out. Chrono-chemotherapy group paclitaxel and cisplatin use the same dosage as conventional chemotherapy group. Paclitaxel was infused intravenously starting at 4 a.m. every day; and cisplatin was infused intravenously at 10-22 a.m. that day for 3 days.

Clinical efficacy and adverse reactions

After 2 cycles of chemotherapy, the quality of life (QOL) score was used to evaluate the QOL of the two groups of patients.

It was assessed according to related descriptions given in the *Response Evaluation Criteria In Solid Tumors* (RECIST). Complete remission (CR) meant complete disappearance of all lesions; partial remission (PR) meant reduction in the sum of the length and diameter of the lesions at baseline by ≥30%; progressed (PD) meant the total length and diameter of the lesions increased by ≥20% at baseline, or new lesions appeared; and stable (SD) meant reduction of lesions did not reach PR, or its increase did not reach PD. The total effective rate was calculated by CR + PR.

Table 1. Data of patients

Item	Chrono-chemotherapy group (n = 30)	Conventional chemotherapy group (n = 30)	*P* value
Gender			0.092
Males	18	14	
Females	12	16	
Age (years old)	43.35 ± 9.48	46.78 ± 9.38	0.073
Histopathological classification of cells			0.192
Squamous cell carcinoma	17	16	
Adenocarcinoma	13	14	
Staging			0.364
II_B	3	3	
III_A	7	6	
III_B	15	17	
IV	5	4	

Adverse reactions were classified into grades I, IV, III, and IV according to the World Health Organization (WHO) grading criteria for adverse reactions [17].

Detection of immune function by FCT

In order to understand the changes in immune function before and after chemotherapy in patients, fasting venous blood samples need to be collected from both groups of patients before and after chemotherapy to measure relevant immunological indicators. Immune function will be assessed using the Beckman-Coulter-Gallios flow cytometer (Beckman, USA). The levels of CD3+, CD4+, CD8+, CD4+CD8+, and CD8+CD28- cells will be analyzed using the system software.

The detection process is as follows: First, 10 μL of fluorescent-labeled monoclonal antibodies (CD45+, CD3+, CD3+CD4+, CD3+CD8+, CD3-CD56+/CD16+, CD19+, CD8+CD28+, and CD8+CD28-) will be taken and placed in separate tubes. Then, 100 μL of peripheral whole blood will be added to each tube, followed by gentle mixing and incubation at room temperature in the dark for 20 minutes. Next, 500 μL of red blood cell lysis solution will be added, thoroughly mixed, and incubated at room temperature in the dark for 15 minutes. After incubation, the samples will be centrifuged at 1500 rpm for 5 minutes, the supernatant will be discarded, and 1 mL of PBS solution will be added for thorough washing. Subsequently, 1 mL of phosphate-buffered saline will be added for thorough mixing, creating a single-cell suspension. Finally, the samples will be analyzed using the flow cytometer to quantify the cell levels of various immune cells within lymphocytes.

Quality control

It should strictly follow the reagent instructions to determine the experimental reaction time and temperature to ensure the accuracy of the results.

CD3+, CD4+, CD8+, CD4+CD8+, and CD8+ CD28- were paired with four-color and two-color fluorescent dyes from Beckman Coulter, USA. The negative samples, single-stained FITC-positive samples, single-stained PE-positive samples, and double-stained positive samples were employed to adjust detection voltage and fluorescence compensation to establish appropriate detection templates.

Statistical analysis

All data were established in Excel database and analyzed using SPSS 21.0. Measurement data and enumeration data were displayed with mean ± standard deviation ($\bar{x} \pm s$) and percentage (%), respectively. The difference was statistically significant at $P<0.05$.

Results

Patients

The chrono-chemotherapy group consisted of 18 males and 12 females (43.35 ± 9.48 years old in average). There were 30 conventional chemotherapy group patients, including 14 males and 16 females, with (46.78 ± 9.38) years old averaged. No great significance was exhibited in baseline data of patients before they received different treatment methods such as gender, age, cell histopathological classification, and staging of the two groups of patients, and they were comparable ($P>0.05$) (**Table 1**).

Table 2. Comparison of clinical efficacy of patients with different treatment methods [n (%)]

Group	CR	PR	PD	SD	Effective rate (CR + PR)
Chrono-chemotherapy group	11 (36.66)	15 (50.00)	3 (10.00)	1 (3.33)	26 (86.66)
Conventional chemotherapy group	3 (10.00)	10 (33.33)	14 (46.66)	3 (10.00)	13 (43.33)
P value					0.021

Comparison of clinical efficacy of two groups

Clinical efficacy comparison between the two groups was shown (**Table 2**). Effective rate of chrono-chemotherapy group was 86.66%, and that of conventional chemotherapy group was 43.33%. The effective rate of the chrono-chemotherapy group was higher than that of the conventional chemotherapy group, presenting a difference with *P<0.05*.

Immune function between two groups of patients

The immune function in the two groups before and after treatment was compared (**Figure 1**).

In the conventional chemotherapy group, CD3+, CD4+, and CD28+ were higher than those before chemotherapy, with *P<0.05*; CD8+ was also higher but exhibited a difference with *P*>0.05. Compared with before chemotherapy, NK cells, B cells, and CD28- decreased with statistically and presented the differences with *P<0.05*, while CD4+/CD8+ with no statistical significance (*P*>0.05). It indicated that conventional chemotherapy could affect the both cellular and humoral immunity of patients, but it was not significant.

In the chrono-chemotherapy group, CD3+, CD4+, CD4+CD8+, B cells, and CD28+ were higher than those before chemotherapy (*P< 0.05*); while CD8+, NK cells, and CD28- decreased with *P<0.05*. It indicated that chrono-chemotherapy can improve the cellular immunity of patients, but had no significant effect on humoral immunity.

PFS and QOL scores

The PFS of patients in the chrono-chemotherapy group was longer (2.56 ± 0.35 years vs 3.29 ± 0.46 years), showing a difference with *P< 0.05*. The QOL score of patients in the chrono-chemotherapy group (51.72 ± 1.89 points) was higher than (64.83 ± 1.54 points) in the conventional chemotherapy group (*P<0.05*) (**Figure 2**).

Adverse reactions

Myelosuppression was manifested as leukopenia, and its incidence in the conventional chemotherapy group (63.33%) was higher than that in the chrono-chemotherapy group (30.00%), showing a difference with *P<0.05*. The main clinical manifestation of gastrointestinal reactions was nausea and vomiting, and its incidence in the conventional chemotherapy group (53.33%) was higher than that of chrono-chemotherapy group (30.00%), showing statistically obvious difference (*P<0.05*). Meanwhile, we observed no visible differences in the reduction of hemoglobin, thrombocytopenia, anemia, diarrhea, peripheral neurotoxicity, and liver and kidney toxicity between the two groups (*P*>0.05) (**Table 3**).

Discussion

Chrono-chemotherapy combines the characteristics of 24-hour circadian changes and chrono-pharmacology, and choosing an appropriate administration time can maximize the chemotherapy effect and reduce the occurrence of toxic reactions [18-20]. Clinical studies have shown that anticancer drugs reach different peaks at different time points, and drug toxicity is also different [21]. The curative effect of shortening the intravenous infusion time from 24 hours to 3 hours is almost the same, and the toxicity is weakened, so the 3-hour intravenous infusion time was selected in this work.

According to in vitro experiments in small animals, within the effective concentration range of the drug, the intensity of the drug's action gradually increases over time, and at the same time, the drug's toxicity also increases [22]. Therefore, according to the pharmacological action and mechanism of paclitaxel, it can exert anticancer and radiotherapy effects on tumor cells. Stoumpos et al. (2021) [23] found in the time toxicology study of paclitaxel that using the same drug dose in normal mice, administration during the light-on period (mice rest period) can significantly reduce the drug

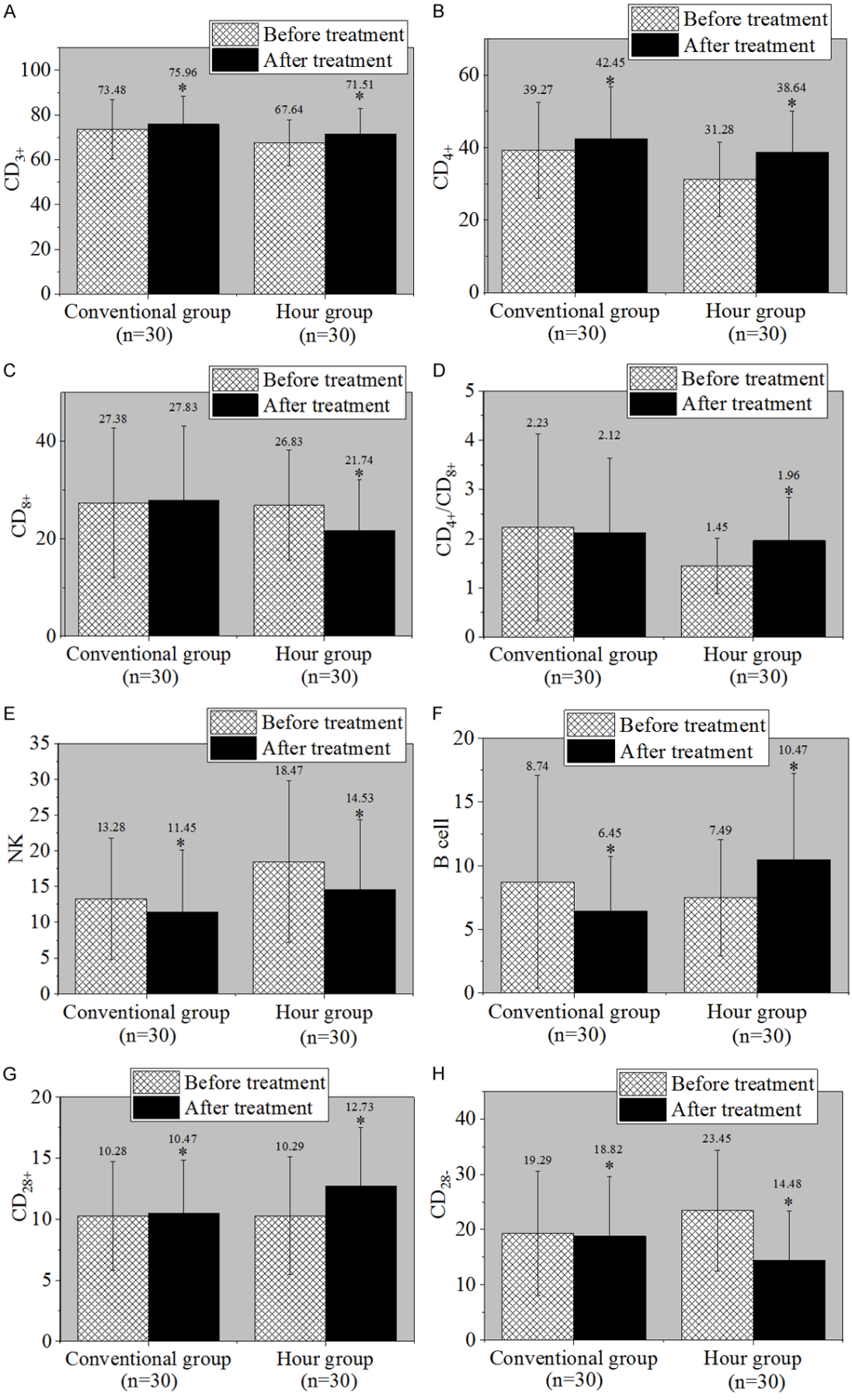
A
Before treatment
After treatment
CD3+
73.48
75.96
67.64
71.51
Conventional group (n=30)
Hour group (n=30)
B
CD4+
39.27
42.45
31.28
38.64
C
CD8+
27.38
27.83
26.83
21.74
D
CD4+/CD8+
2.23
2.12
1.45
1.96
E
NK
13.28
11.45
18.47
14.53
F
B cell
8.74
6.45
7.49
10.47
G
CD28+
10.28
10.47
10.29
12.73
H
CD28-
19.29
18.82
23.45
14.48

Figure 1. Immune function of patients. A: Lymphocytes CD3+; B: Lymphocytes CD4+; C: Lymphocytes CD8+; D: CD4+/CD8+; E: NK cells; F: B cells; G: Lymphocytes CD28+; H: Lymphocytes CD28-. Note: * indicated *P<0.05* vs the levels before treatment.

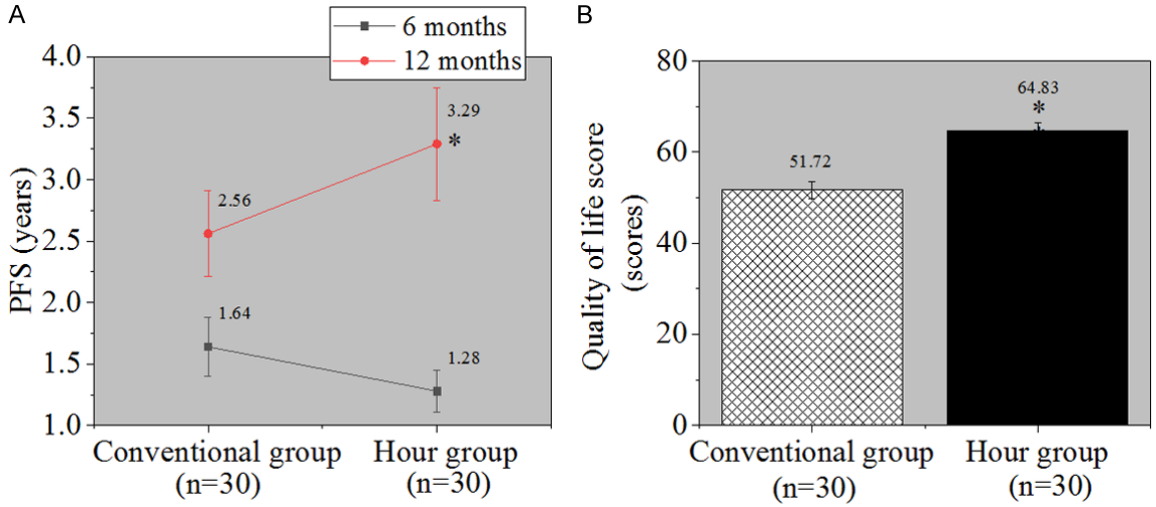

Figure 2. Comparison of PFS and QOL scores. A: Comparison of PFS; B: Comparison of QOL score. Note: * indicated *P<0.05* vs conventional chemotherapy group.

Table 3. Comparison of two groups of adverse reactions

Item	Conventional chemotherapy group (n = 30)				Incidence (%)	Chrono-chemotherapy group (n = 30)				Incidence (%)
	Grade I	Grade II	Grade III	Grade IV		Grade I	Grade II	Grade III	Grade IV	
Leukopenia	10	6	2	1	63.33	5	3	1	0	30.00*
Thrombocytopenia	6	3	1	0	33.33	5	2	1	0	26.66
Anemia	7	2	1	0	33.33	4	3	0	0	23.33
Feel sick and vomit	8	3	3	2	53.33	6	2	1	0	30.00*
Hepatotoxicity	7	2	1	0	33.33	6	1	1	0	26.66
Nephrotoxicity	2	0	0	0	6.66	2	1	0	0	10.00
Decreased hemoglobin	6	4	2	0	40.00	4	3	0	0	23.33
Diarrhea	3	2	0	0	16.66	2	0	0	0	6.66
Peripheral neurotoxicity	8	2	1	0	36.66	3	0	0	0	10.00

Note: * indicated *P<0.05* vs conventional chemotherapy group.

toxicity and improve the tolerance and anticancer activity of mice. This shows that paclitaxel is suitable for administration at night when patients are resting, which can improve its efficacy. This experiment was administered at 4 a.m. for the best clinical efficacy. Cisplatin produces a large number of free radicals in the body, which in turn triggers lipid peroxidation in various important organs of the patient's body, resulting in the occurrence of toxic reactions [24-26]. Administered at 10-22 o'clock every day, the peak drug concentration was predicted to appear at 16 o'clock, with better tolerance and lower toxicity. The TP regimen is the first-line chemotherapy regimen for the treatment of NSCLC, and its efficacy and safety have been proven.

Chemotherapy not only has a killing effect on nausea tumor cells, but also has a killing effect on highly sensitive lymphocytes, which directly affects the cellular immune mechanism of the body [27]. This work further explored the effects of TP regimen chrono-chemotherapy and con-

ventional chemotherapy on the immune function of NSCLC patients. Under normal circumstances, the immune function and state of the body are tightly related to the occurrence, development, and prognosis of malignant tumors, which can improve the immune function of patients and help control the tumor by regulating the immune function of the body. Li et al found that CD4+, CD4+/CD8+, and CD56+ cells were significantly increased in NSCLC patients after chemotherapy. In this work, FCT was employed to detect the immune function of the patients. CD3+, CD4+, CD4+CD8+, B cells, and CD28+ of the chrono-chemotherapy group increased compared with those before chemotherapy (*P<0.05*); while CD8+, NK cells, and CD28- were lower than those before chemotherapy, and the differences were statistically significant (*P<0.05*) [28]. Such results are consistent with the above experimental results. This shows that chrono-chemotherapy can improve the patient's cellular immune function, directly kill tumor cells, and relieve the tumor's immune suppression on the body. In addition, chrono-chemotherapy can be administered according to the patient's biological rhythm, avoiding damage to the lymphatic system. There are many genetic, biochemical, physiological, and epigenetic findings related to lung cancer [29-40], as well as findings from these areas of research related to other lung complications [41-55].

In this work, chrono-chemotherapy and conventional chemotherapy were formulated according to the chronotherapy in modern science, and the clinical efficacy of the two chemotherapy methods was compared. We observed that the effective rate of patients receiving the chrono-chemotherapy was higher than that with conventional chemotherapy, and the difference was statistically significant (*P<0.05*). Patients in the chrono-chemotherapy group had longer PFS (2.56 ± 0.35 years) than those in the conventional chemotherapy group (3.29 ± 0.46 years) (*P<0.05*). The QOL score of patients in the chrono-chemotherapy group (51.72 ± 1.89 points) was better than that in the conventional chemotherapy group (64.83 ± 1.54 points) (*P<0.05*). Myelosuppression was manifested as leukopenia, and the incidence of conventional chemotherapy group (63.33%) was higher than that of chrono-chemotherapy group (30.00%) (*P<0.05*). The main clinical manifestations of gastrointestinal reactions were nausea and vomiting, and the incidence of conventional chemotherapy group (53.33%) was more common than that of chrono-chemotherapy group (30.00%) (*P<0.05*). It shows that chrono-chemotherapy therapy of NSCLC patients has small side effects and high safety, and can effectively improve the QOL of patients.

To sum up, TP regimen chrono-chemotherapy therapy could improve the cellular immune function of NSCLC patients, reduce the occurrence of adverse reactions, and improve the QOL of patients. As an effective means for the treatment of NSCLC, it could be promoted and used in clinical practice. Zhang et al. (2021) [56] divided nasopharyngeal carcinoma patients into a timely chemotherapy group and a conventional chemotherapy group. They compared the levels of peripheral blood T lymphocyte subpopulations before and after treatment and followed up to record long-term survival rates and disease progression. The results showed that the total effective rate of the timely chemotherapy group was 96%, while the conventional chemotherapy group was 94.7%. Additionally, 6 months after treatment, the levels of CD3+, CD4+, CD8+, CD4+/CD8+, CD16+CD56+, and CD19+ T cells in the peripheral blood of patients were significantly lower than before treatment. The CD16+CD56+ T cell level in the timely chemotherapy group was significantly lower than that in the conventional chemotherapy group. Furthermore, the follow-up results showed that the 3-year overall survival rate of the timely chemotherapy group was 73.3%, and the 3-year PFS was 60.0%, while the conventional chemotherapy group had a 3-year overall survival rate of 69.3% and a 3-year PFS of 62.7%, with no significant difference. This experiment indicates that timely chemotherapy has a higher treatment effective rate in treating nasopharyngeal carcinoma, slightly higher than conventional chemotherapy. This suggests that timely chemotherapy may have certain advantages in controlling disease progression and improving the condition of nasopharyngeal carcinoma patients. Additionally, both treatment methods had an impact on patients' immune systems, leading to a decrease in immune cell numbers. However, the level of CD16+CD56+ T cells after treatment was significantly lower in the timely chemotherapy group than in the conventional

chemotherapy group, which may be related to the different effects of timely chemotherapy on the immune system. However, in terms of the 3-year survival rate and PFS rate, the effects of timely chemotherapy and conventional chemotherapy were relatively similar, with no significant difference. This indicates that both treatment methods can be effective choices for treating nasopharyngeal carcinoma, and clinicians can choose the appropriate treatment plan based on individual patient circumstances and personalized needs. Both nasopharyngeal carcinoma and lung cancer are malignant tumors, and they may be sensitive to chemotherapy drugs. Immunotherapy has shown certain efficacy in both types of cancer, so the results of treating nasopharyngeal carcinoma may be extrapolated to the treatment of lung cancer to some extent. The treatment indicators used in this experiment, such as overall survival rate and PFS, are commonly used indicators in cancer treatment research. These indicators are of great significance for evaluating treatment effects in different types of cancer. Therefore, if the treatment methods for both types of cancer show similar results in these indicators, it is possible to assume that they may have similar trends in treatment effects. However, it is important to emphasize that although the experimental results may be applicable to other types of cancer, caution should still be exercised in generalizing them. Different types of cancer may have significant differences in pathological characteristics, biological behavior, and treatment response. Therefore, while the experimental results have some reference value, further comprehensive consideration and more clinical research and validation are needed when applying them to other types of cancer based on specific circumstances.

Conclusions

In this work, we detected the changes of immune function cells in each patient before and after chemotherapy to observe the adverse reactions during the curative effect and the survival rate of patients and to explore the clinical efficacy of chrono-chemotherapy and conventional chemotherapy of TP regimen in NSCLS patients. The chrono-chemotherapy could improve the cellular immune function of NSCLS patients, prolong the survival period of patients, improve the level of quality of life, and reduce side effects. In addition, the chrono-chemotherapy therapy of NSCLC patients has small side effects and high safety, and can effectively improve the QOL of patients.The shortcoming of this work was that the clinical research time was limited, the survival rate for a longer time of chrono-chemotherapy treatment of NSCLC patients was not perfect, and the follow-up time needed to be extended in the later stage to further confirm the conclusion.

Disclosure of conflict of interest

None.

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