International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

OPEN ACCESS International Journal of Pharmacology

ISSN 1811-7775
DOI: 10.3923/ijp.2022.906.914

Research Article
Clinical Efficacy and Prognostic Influence of Qikui Decoction in Adjuvant Chemotherapy for Advanced Non-Small Cell Lung Carcinoma

Jie Xu, Na Xiao, Hailang He and Xianmei Zhou

Department of Pulmonary and Critical Care Medicine, Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu 210009, China

Abstract

Background and Objective: Improving patient outcomes and treatment efficiency and increasing survival rate are still the hurdles that clinical workers need to solve. The purpose of this study was to inquire into the clinical efficacy and prognostic influence of Qikui decoction in adjuvant chemotherapy for advanced Non-Small Cell Lung Carcinoma (NSCLC). **Materials and Methods:** One hundred patients with advanced NSCLC who received chemotherapy with paclitaxel (PTX) and cisplatin (DDP) in hospitals were selected as the research participants. Among them, 50 patients were treated with PTX combined with DDP as a control group (CG) and another 50 patients were additionally given Qikui decoction during chemotherapy as an observation group (OG). The following items were observed in both arms: Clinical efficacy, adverse reactions (ARs), serum tumour markers (STMs), liver and kidney function, immune function, prognosis and survival. **Results:** After treatment, the curative effect was higher ($p = 0.043$) and the incidence of ARs ($p = 0.032$) was lower in OG as compared to CG, CEA, NSE and CYFRA211 decreased in both groups and were lower in OG ($p<0.05$), Scr, BUN and ALT reduced in both arms, with more evident reductions in OG ($p<0.05$), $CD4^+$ and $CD4^+/CD8^+$ increased while CD^{8+} decreased in both arms ($p<0.05$) and the alterations were more obvious in OG ($p<0.05$), OG also showed better quality of life, prognosis and survival than CG ($p<0.05$). **Conclusion:** Qikui decoction in adjuvant chemotherapy for advanced NSCLC has a definite clinical effect and can improve the prognosis of patients.

Key words: Non-small cell lung carcinoma, chemotherapy, Qikui decoction, clinical efficacy, prognosis

Citation: Xu, J., N. Xiao, H.H. and X. Zhou, 2022. Clinical efficacy and prognostic influence of Qikui decoction in adjuvant chemotherapy for advanced non-small cell lung carcinoma. Int. J. Pharmacol., 18: 906-914.

Corresponding Author: Xianmei Zhou, Department of Pulmonary and Critical Care Medicine, Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, 210009, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Lung cancer (LC), originating from bronchial mucosa or glands of the lungs, is one of the commonly seen malignancies in clinic[1]. It has always been in a high incidence state in China, with a mortality ranking first among malignancies[2], seriously compromising people's health and life. As the number one killer of modern tumours, LC has great harm, among which Non-Small Cell Lung Carcinoma (NSCLC) is the dominant type[3], accounting for more than 85% of LC[4]. However, for the majority of patients, the disease is not detected until it has progressed to the middle and late stages because of the insidious early symptoms, which leads to the missing of the best time for surgical resection[5]. At this stage, chemotherapy is the mainstay of treatment for advanced NSCLC, which utilized cisplatin (DDP) and other regimens to kill tumour cells and reduce tumour cell DNA synthesis, to control the disease progression[6]. However, long-term chemotherapy predisposes patients to drug resistance. Looking up the previous data, it is also found that chemotherapy will damage the immune function of patients to a certain extent, resulting in adverse prognosis and affecting patient survival[7]. Therefore, improving patient outcomes and treatment efficiency and increasing survival rate are still the hurdles that clinical workers need to solve.

In recent years, there have been increasing clinical trials and basic research on the treatment of LC with Chinese medicine by using the theory of traditional Chinese medicine (TCM) and the method of combining syndrome differentiation and disease differentiation, which provides new ideas and approaches for LC treatment[8]. Qikui recipe is a prescription summed up by Professor Zhou Zhongying, a master of Chinese medicine, after years of experience. It is composed of various TCMs such as *Radix Astragali* preparata*, Solanum nigrum* and *Codonopsis pilosula*, with the effects of invigorating qi, promoting blood circulation, detoxifying and resolving stagnation[9]. Previous studies have concluded that the basic syndrome types of advanced NSCLC are mainly weakened body resistance and toxic-stasis[10]. Based on the theory of Qikui recipe in TCM, speculate that Qikui decoction in adjuvant chemotherapy for advanced NSCLC, combined with TCM and western medicine, may have unique therapeutic advantages in treating the disease. This research provides a more effective scheme and reference for clinical treatment of advanced NSCLC and improves the clinical treatment level of LC.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Pulmonary and Critical Care Medicine, Jiangsu Province Hospital of Chinese Medicine, Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China from May, 2019 to January, 2020.

Patient data: The study population comprised 100 patients with advanced NSCLC treated with paclitaxel (PTX) combined with cisplatin (DDP) in hospital from May, 2019 to January, 2020. According to different therapeutic regimens, they were allocated into two groups: The control group (CG, n = 50) treated with PTX+DDP and the observation group (OG, n = 50) supplemented with Qikui decoction during chemotherapy based on CG. All the enrolled patients signed the informed consent to participate after this study was ratified by the Hospital Ethics Committee.

Eligibility criteria: Patients were included according to the following criteria: All the patients (18-85 years old) met the diagnostic criteria of western medicine for advanced NSCLC (referring to the Clinical Diagnosis and Treatment Guidelines-Tumors) and were confirmed as stage IV according to the American Joint Committee on Cancer (8th edition), with normal bone marrow function, liver and kidney function and lung function, complete case data and no contraindication to chemotherapy.

In contrast, those who met any of the following criteria were excluded: Patients with infection, intestinal obstruction, or internal metastasis requiring radiotherapy, pregnant and lactating women, patients with obvious myelosuppression and dysfunction of kidney, lung, liver and kidney, patients with poor compliance, patients with disabilities as prescribed by law, people with allergic constitution who were allergic to the ingredients of the medication, patients who cannot take medicine as prescribed and cannot determine the efficacy or those who were participating in other clinical trials.

Methods: The CG received systemic chemotherapy with a two-drug regimen containing platinum: Taxol+DDP was used for 4 cycles, once every 3 weeks, followed by gemcitabine for 2 cycles, once every 3 weeks, for 5 months. OG: Qikui decoction, the dosage of which was increased or decreased according to the symptoms of patients, was given to patients orally based on CG. The 300 mL decoction was administrated orally in the morning and evening and the course of treatment was 5 months. The empirical formula of Qikui recipe contains *Radix Astragali* preparata (15 g), *Solanum nigrum* (10 g), radix *Codonopsis* (15 g), *Ganoderma lucidum* (15 g), *Rhizoma polygonati preparata* (15 g), *Fructus ligustri lucidi* (15 g), *Caulis spatholobi* (15 g), *Polyporus umbellatus* (15 g), fried coix seed (15 g), sun *Euphorbia* herb (9 g), *Hedyotis diffusa* (15 g), *Pseudobulbus cremastraeseu pleiones* (9 g),

Curcuma zedoary (10 g) and Radix *Glycyrrhizae preparata* (5 g). Note: Except for the study medication, other Traditional Chinese and western drugs for NSCLC and other treatments related to the disease were prohibited during the observation period.

Follow-up for prognosis: The patients enrolled in this study were followed up for one year via hospital re examination, to record their prognoses and survival.

Endpoints: Primary endpoints: Clinical efficacy, adverse reactions (ARs), serum tumour markers (STMs), carcinoma embryonic antigen (CEA) neuron specific enolase (NSE) cytokeratin-19 fragment, CYFRA211 and patient prognosis and survival. Secondary endpoints: Liver function, alanine aminotransferase (ALT), kidney function, blood urea nitrogen, (BUN) serum creatinine (Scr), immune function ($CD4^+$, $CD8^+$, $CD4^+/CD8^+$) and prognostic quality of life.

Statistical methods: All calculations were performed with the use of SPSS18.0 and all graphs were drawn by Graphpad8 software and the results were checked twice. Categorical data, such as clinical efficacy and incidence of adverse reactions, were given (percentages) and the differences were analyzed with the Chi-square test. Quantitative data and concentration were given (Mean±Standard Deviation), the inter-group comparison adopted T-test and the multiple time point comparison employed repeated measures ANOVA and Bonferroni back testing. The significance level was assumed at $p<0.05$.

RESULTS

Comparison of general information between the two groups: Comparing the general information between the two groups, it was found that there were no significant differences in age, sex, Body Mass Index (BMI), lesion diameter ($p>0.05$) in Table 1, confirming the comparability between the two groups.

Comparison of clinical efficacy between the two groups: In OG, 30.00% of patients had a complete response, 52.00% had a partial response, 14.00% had stable disease, 4.00% had progressive disease and the total effective rate was 82.00%. In CG, complete response was observed in 16.00% of patients, partial response in 48.00% of patients, stable disease in 22.00% of patients and progressive disease in 14.00% of patients. The overall response rate in OG (82.00%) was higher than that in CG (64.00%) ($p>0.05$) in Table 2.

Table 1: General data of patients (n (%))

	OG (n = 50)	CG (n = 50)	t or χ^2	p-value
Age (years)	64.5±5.7	65.3±5.6	0.708	0.481
Gender				
Male	29 (58.00)	26 (52.00)	0.364	0.547
Female	21 (42.00)	24 (48.00)		
BMI (KG cm^{-2})	26.52±3.05	26.86±3.12	0.551	0.583
Diameter of lesion (cm)	3.68±0.26	3.71±0.30	0.534	0.594
Clinical staging				
III	9 (18.00)	11 (22.00)	0.250	0.617
IV	41 (82.00)	39 (78.00)		
Residence				
Urban	36 (72.00)	32 (64.00)	0.735	0.391
Rural	14 (28.00)	18 (36.00)		
History of smoking				
Yes	30 (60.00)	28 (56.00)	0.164	0.685
No	20 (40.00)	22 (44.00)		
Family medical history				
Yes	4 (8.00)	6 (12.00)	0.444	0.505
No	46 (92.00)	44 (88.00)		
Ethnicity				
Han	48 (96.00)	50 (100.00)	2.041	0.153
Ethnic minorities	2 (4.00)	0 (0.00)		

Table 2: Comparison of clinical efficacy between the two groups (n (%))

	OG (n = 50)	CG (n = 50)	χ^2	p-value
Complete response	15 (30.00)	8 (16.00)		
Partial response	26 (52.00)	24 (48.00)		
Stable disease	7 (14.00)	11 (22.00)		
Progressive disease	2 (4.00)	7 (14.00)		
Overall response rate (%)	82.00	64.00	4.110	0.043

Table 3: Comparison of adverse reactions between the two groups (n (%))

	OG (n = 50)	CG (n = 50)	χ^2	p-value
Nausea and vomiting	5 (10.00)	9 (18.00)		
Leukopenia	3 (6.00)	5 (10.00)		
Liver and kidney dysfunction	2 (4.00)	4 (8.00)		
Thrombocytopenia	1 (2.00)	3 (6.00)		
Incidence of adverse reactions (%)	22.00	42.00	4.596	0.032

Comparison of ARs between the two groups: In OG, 10.00% of patients had nausea and vomiting, 6.00% of patients had leukopenia, 4.00% of patients had liver and kidney dysfunction and 2.00% had thrombocytopenia. In CG, 18.00% of patients suffered from nausea and vomiting, 10.00% suffered from leukopenia, 8.00% suffered from liver and kidney dysfunction and 6.00% suffered from thrombocytopenia. The incidence of ARs in OG (22.00%) was lower than that in CG (42.00%) ($p>0.05$) in Table 3.

Comparison of the levels of STMs between the two groups: Before treatment, the CEA in OG was 13.15±2.54 ng mL^{-1}, which was not different from that of 13.22±2.61 ng mL^{-1} in CG ($p>0.05$). After treatment, the CEA decreased in both groups and was lower in OG 5.56±1.02 ng mL^{-1} compared with CG 7.43±1.04 ng mL^{-1} ($p<0.05$) in Fig. 1a. Before treatment, the NSE in OG was 24.23±3.25 ng mL^{-1}, which was not different from that of 24.15±3.18 ng mL^{-1} in CG ($p>0.05$).

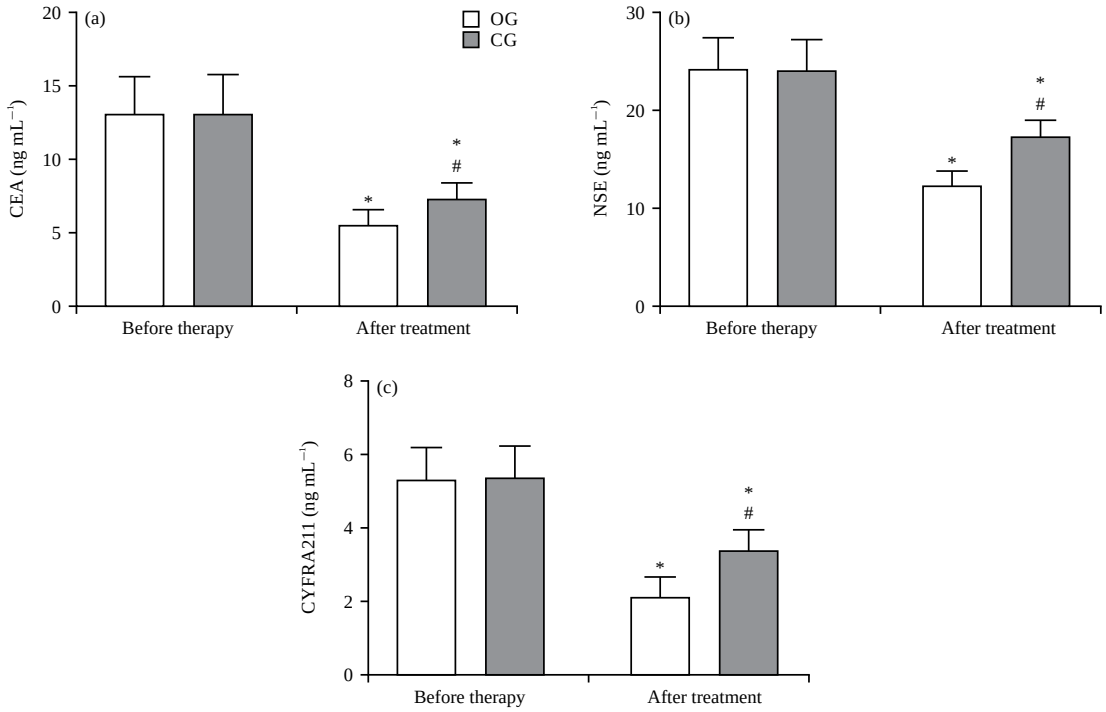

Fig. 1(a-c): Comparison of the levels of serum tumour markers between the two groups before and after treatment, (a) CEA levels, (b) NSE levels and (c) CYFRA211 levels

Before treatment, there was no difference between the two groups, after treatment, it was lower than before treatment and OG was lower than CG, *p<0.05: Compared with before treatment and #p<0.05: Compared with OG

After treatment, the NSE decreased in both groups and was lower in OG 12.36±1.51 ng mL^{-1} compared with CG 17.41±1.67 ng mL^{-1} ($p<0.05$) in Fig. 1b. Before treatment, the CYFRA211 in OG was 5.32±0.87 ng mL^{-1}, which was not different from that of 5.38±0.85 ng mL^{-1} in CG ($p>0.05$). After treatment, the CYFRA211 decreased in both groups and was lower in OG 2.12±0.54 ng mL^{-1} compared with CG 3.41±0.55 ng mL^{-1} ($p<0.05$) in Fig. 1c. It can be seen that the levels of STMs decreased in both groups after treatment, with more significant reductions in OG compared with CG.

Comparison of liver and kidney function between the two groups: Before treatment, the Scr in OG was 156.27±25.73 μmol L^{-1}, which was not different from that of 157.31±24.24 μmol L^{-1} in CG ($p>0.05$). After treatment, the Scr decreased in both groups and was lower in OG 112.31±23.10 μmol L^{-1} compared with CG 133.82±24.33 μmol L^{-1} ($p<0.05$) in Fig. 2a. Before treatment, the BUN in OG was 11.67±2.31 mmol L^{-1}, which was not different from that of (11.82±2.34 mmol L^{-1}) in CG ($p>0.05$). After treatment, the BUN decreased in both groups and was lower in OG 7.13±1.32 mmol L^{-1} compared with CG 8.79±1.45 mmol L^{-1} ($p<0.05$) in Fig. 2b. Before treatment, the ALT in OG was 89.67±20.21 U L^{-1}, which was not different from that of 91.23±19.78 U L^{-1} in CG ($p>0.05$). After treatment, the ALT decreased in both groups and was lower in OG 56.25±15.43 U L^{-1} compared with CG 67.91±15.36 U L^{-1} ($p<0.05$) in Fig. 2c. The results indicated that the liver and kidney function of both groups was effectively improved after treatment, but the improvement was better in OG compared with CG.

Comparison of immune function between the two groups: The immune function of patients in the two groups was evaluated by detecting the levels of T lymphocyte subsets. The results showed that the $CD4^+$ of OG before treatment was 31.15±6.52%, which was not different from that of CG 31.17±6.65% ($p>0.05$). After treatment, $CD4^+$ increased in both groups and was higher in OG 53.66±7.39% compared with CG 44.76±6.87% ($p<0.05$) in Fig. 3a. Before treatment, the $CD8^+$ in OG was 30.57±4.23%, which was not different from that of 30.55±4.21% in CG ($p>0.05$). After treatment, the $CD8^+$ decreased in both groups and was lower in OG 18.56±3.16% compared with CG 25.69±3.48% ($p<0.05$) in Fig. 3b. The immune function of patients in the two groups was evaluated by detecting the levels of T lymphocyte subsets. The results showed that the $CD4^+/CD8^+$ of OG before treatment was 1.16±0.17, which was not different from

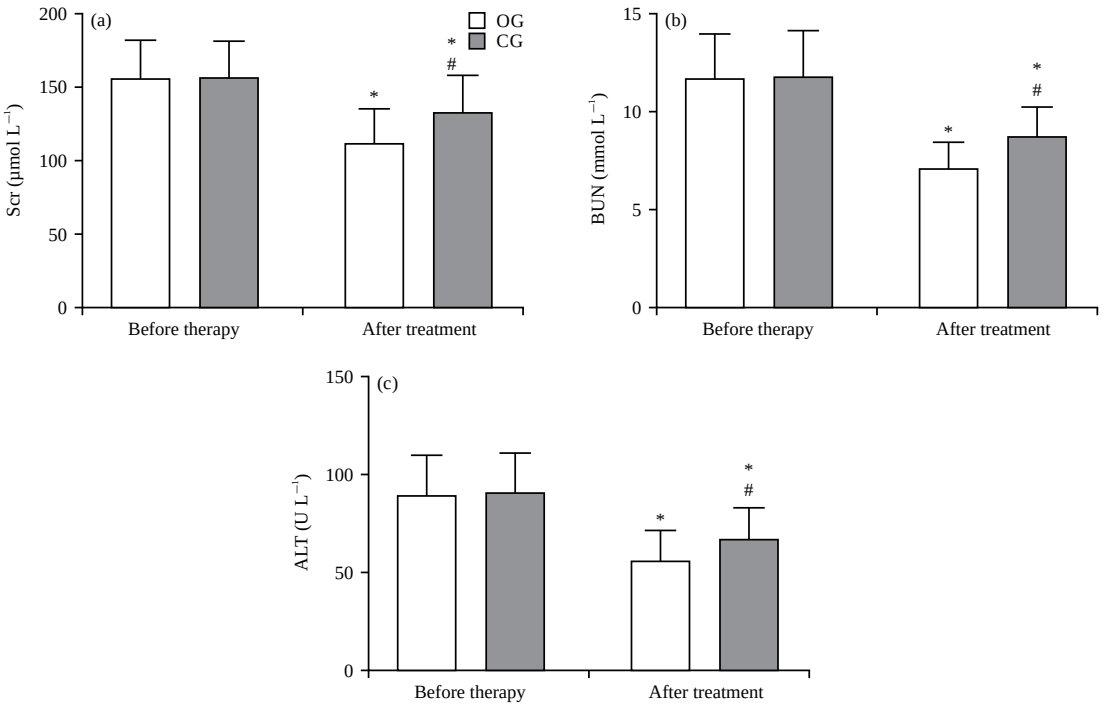

Fig. 2(a-c): Comparison of liver and kidney function between the two groups before and after treatment, (a) Scr level, (b) BUN level, (c) ALT level

Before treatment, there was no difference between the two groups, after treatment, it was lower than before treatment and OG was lower than CG, *p<0.05: Compared with before treatment and #p<0.05: Compared with OG

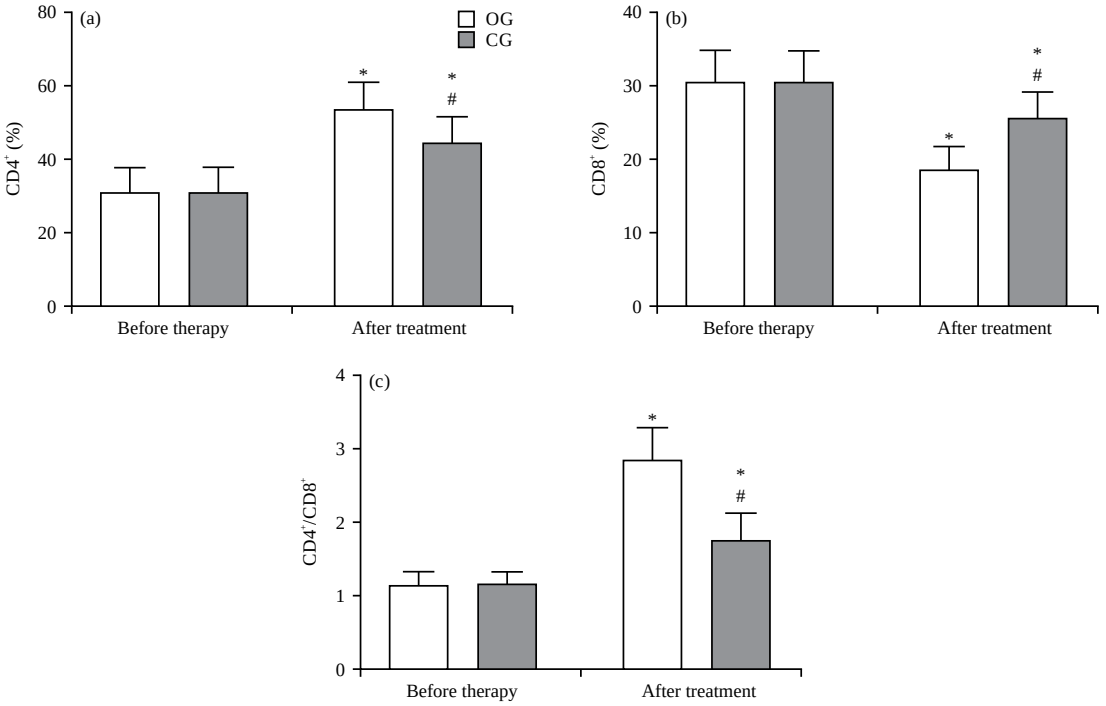

Fig. 3(a-c): Comparison of immune function between the two groups, (a) Proportion of $CD4^+$ T lymphocyte subsets, (b) Proportion of $CD8^+$ T lymphocyte subsets and (c) Proportion of $CD4^+/CD8^+$ T lymphocyte subsets

There was no difference between the two groups before treatment, after treatment, $CD4^+$ and $CD4^+/CD8^+$ increased in both groups and were higher in the observation group compared with the control group, $CD8^+$ decreased in both groups and was lower in the observation group compared with the control group, *p<0.05: Compared with before treatment and #p<0.05: Compared with OG

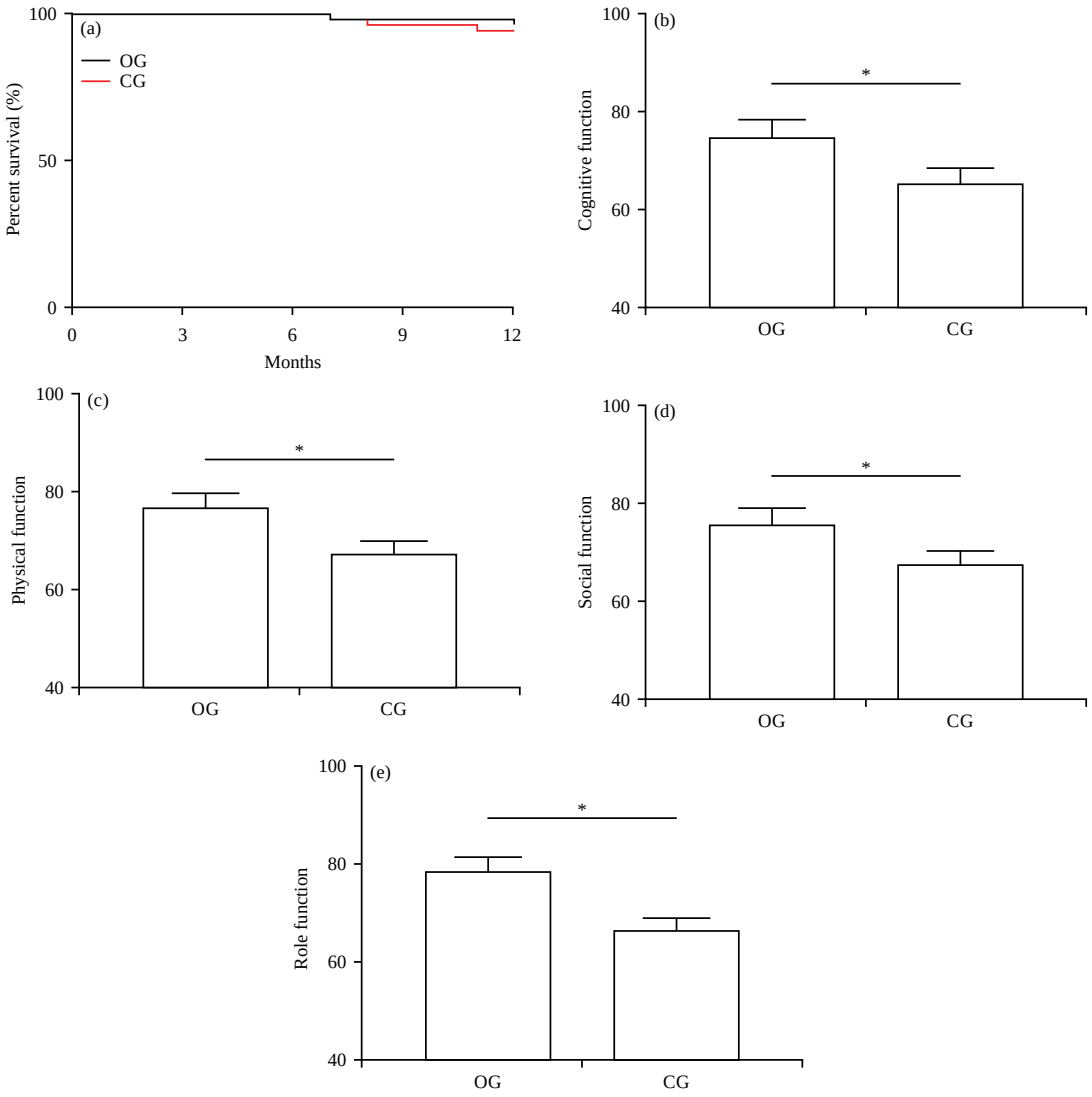

Fig. 4(a-e): Comparison of prognostic survival and quality of life scores between the two groups, (a) Prognostic 1 year survival curves of the two groups, (b) Cognitive function scores, (c) Physical function scores, (d) Social function scores and (e) Role function scores

There was no difference in the overall survival rate between the two groups, but the scores of all dimensions of quality of life in the observation group were higher than those in the control group and *p<0.05: Comparison between the two groups

that of CG 1.18±0.15 (p>0.05). After treatment, $CD4^+/CD8^+$ increased in both groups and was higher in OG 2.85±0.43 compared with CG 1.76±0.36 (p<0.05) Fig. 3c. The results suggest that the immune function of the two groups was enhanced after treatment and was better in OG compared with CG.

Comparison of prognostic survival and quality of life between the two groups: During the 1 year follow-up, 47 cases in OG and 49 cases in CG were successfully followed up. The overall 1 year survival rate of OG was 96.00%, while that of CG was 94.00%, with no significant difference between the two groups (p<0.05) (Fig. 4a). The evaluation of the prognostic quality of life showed that the score of cognitive function in OG was 74.67±3.78, which was higher than that in CG 65.61±2.93 (p<0.05) (Fig. 4b). The score of physical function in OG was 76.75±2.94, which was also higher than that in CG 67.55±2.38 (p<0.05) (Fig. 4c). The score of social function in OG 75.73±3.31 was higher than that in CG 67.51±2.76 (p<0.05) (Fig. 4d). The score of role function in OG was 78.55±2.85, which was also higher than that in CG 66.39±2.54 (p<0.05) (Fig. 4e). The above data showed that the prognostic quality of life in OG was significantly better than that in CG.

DISCUSSION

With the acceleration of China's industrialization, the morbidity and mortality of LC have taken the first place among malignant tumors[11]. So, it has become an important subject which is in urgent need of seeking a breakthrough in clinic. LC can be divided into SCLC and NSCLC, among which the later occupies a greater proportion, accounting for about 85% of all LCs[12]. At present, due to the non-specific early symptoms and the limitations of early diagnosis means, most patients cannot get timely diagnosis and treatment, resulting in approximately 75% of the cases developing into advanced LC once diagnosed[13]. Currently, the major clinical means for NSCLC are surgical resection as well as radiotherapy and chemotherapy[2]. However, because the disease progresses too quickly for surgical treatment, platinum-based chemotherapy is usually selected for advanced patients[14]. Whereas, its curative effect has reached a bottleneck with a relatively higher risk of ARs, so it is difficult for patients to obtain greater benefits[15]. In recent years, there are accumulating clinical trials and basic research on treating LC with TCM theory, which provides new ideas and means for treating LC[16]. Consulting relevant data, found that Qikui recipe has many effects such as detoxification and anticancer action[17]. Therefore, it is speculated that its application in the chemotherapy process of advanced NSCLC patients can improve the therapeutic efficacy of patients. Therefore, a detailed analysis is carried out and the results are as follows.

This time, we compared the curative efficacy of PTX+DDP combined with Qikui decoction and PTX+DDP alone for advanced NSCLC patients. It was found that the overall response rate of OG assisted with Qikui decoction was notably higher than that of CG, which suggested that Qikui decoction in adjuvant chemotherapy contributes to higher efficacy in advanced NSCLC patients. In addition, the incidence of ARs was found to be noticeably lower in OG. Due to the weakened body function and poor immune capacity of patients with advanced NSCLC, the metabolism rate of chemotherapy drugs is slow, which may cause serious ARs[18]. The experimental results reflect the application value of Qikui decoction, that is, the auxiliary use of Qikui decoction not only reversed the adverse effects of chemotherapy on advanced NSCLC patients, such as drug resistance but also improved the treatment safety. Looking up the previous data, it is found that Qikui decoction has multiple therapeutic effects, such as invigorating the spleen, moistening the lung, tonifying the kidney and replenishing and activating blood. Besides, it can detoxify and disperse stagnation, detoxicate and resist cancer, eliminate stagnation and relieve pain[19]. Speculated that it may be the synergistic effect of various drugs that have played a role in the treatment of patients with advanced NSCLC undergoing chemotherapy. Then, we detected the STMs and found no significant difference in CEA, NSE and CYFRA211 levels between the two arms before treatment, whereas, the above STMs decreased in both arms after treatment, especially in OG. The CEA is the earliest tumour marker related to LC, which can effectively reflect the disease progression of patients[20]. The NSE is widely found in nerve tissues and neuron cells, while CYFRA211 will be shed in the process of tumour cell differentiation[21]. Therefore, the results suggest that the condition of the two groups has been controlled to some extent after treatment, while the disease control degree of OG assisted with Qikui decoction is better, demonstrating that Qikui decoction is conducive to reducing the blood toxicity after chemotherapy, thus improving the chemotherapy effect of patients. Apart from that, we found that Scr, BUN and ALT, which differed insignificantly before therapy, reduced in both arms after treatment, with lower parameters in OG. This also confirms that Qikui decoction is more effective in improving the physical function of patients with advanced NSCLC. Affected by the disease, the liver and kidney function will be compromised by various factors such as treatment to cause abnormalities, plus the ARs will often promote the deterioration of the disease and reduce the therapeutic effect, resulting in adverse prognosis[22]. Consequently, it is particularly important to prevent abnormal reactions of body functions. Due to the poor physical fitness, multiple underlying diseases and poor tolerance to chemoradiotherapy, chemotherapy will seriously affect the immune function of patients with advanced NSCLC and increase the risk of complications[23]. However, observing the levels of $CD4^+$, $CD8^+$, $CD4^+/CD8^+$ lymphocyte subsets in patients before and after treatment, it was found that the immune function of patients in OG was improved after treatment. It suggests that the combined use of Qikui decoction can effectively improve the immune function of advanced NSCLC patients, reduce the incidence of other ARs and validly improve their quality of life. Finally, we followed up and evaluated the quality of life, prognosis and survival rate of patients and determined better results in OG, which further supported the above experimental results and reflected the research significance of this experiment.

However, due to limited conditions, there are still some shortcomings in this experiment. For example, the study period is too short to analyze the long-term prognosis of patients. Besides, PTX and DDP are not the only clinically used chemotherapy drugs, so also need to incorporate more drugs to improve our comprehensiveness. Furthermore, due to the lack of basic experiments, we cannot judge the exact mechanism of its action on patients. This study will make a more perfect experimental analysis as soon as possible to get more effective experimental results for clinical reference.

CONCLUSION

To sum up, Qikui decoction in Adjuvant Chemotherapy for advanced NSCLC has definite clinical efficacy and can improve patient prognosis.

SIGNIFICANCE STATEMENT

This study discovered the Qikui decoction can effectively improve the immune function that can be beneficial for NSCLC patients. This study will help the researchers to uncover the critical areas of Qikui decoction can be used in tumours therapy that many researchers were not able to explore. Thus a new theory on Traditional Chinese decoction drug treating NSCLC may is arrived at.

ACKNOWLEDGMENT

This work was supported by the Science and Technology Project of Jiangsu Traditional Chinese Medicine Hospital (NO.Y2020CX06) and National Natural Science Foundation (81673936).

REFERENCES

1. Schabath, M.B. and M.L. Cote, 2019. Cancer progress and priorities: Lung cancer. Cancer Epidemiol. Biomarkers Prev., 28: 1563-1579.
2. de Sousa, V.M.L. and L. Carvalho, 2018. Heterogeneity in lung cancer. Pathobiology, 85: 96-107.
3. Jones, G.S. and D.R. Baldwin, 2018. Recent advances in the management of lung cancer. Clin. Med., 18: s41-s46.
4. Alexander, M., S.Y. Kim and H. Cheng, 2020. Update 2020: Management of non-small cell lung cancer. Lung, 198: 897-907.
5. Ruiz-Cordero, R. and W.P. Devine, 2020. Targeted therapy and checkpoint immunotherapy in lung cancer. Surg. Pathol. Clin., 13: 17-33.
6. Bade, B.C. and C.S.D. Cruz, 2020. Lung cancer 2020: Epidemiology, etiology, and prevention. Clinics Chest Med., 40: 1-24.
7. Hoy, H., T. Lynch and M. Beck, 2019. Surgical treatment of lung cancer. Crit. Care Nurs. Clin. North Am., 31: 303-313.
8. Su, X.L., J.W. Wang, H. Che, C.F. Wang and H. Jiang *et al*., 2020. Clinical application and mechanism of traditional Chinese medicine in treatment of lung cancer. Chin. Med. J., 133: 2987-2997.
9. Henamayee, S., K. Banik, B.L. Sailo, B. Shabnam and C. Harsha *et al*., 2020. Therapeutic emergence of Rhein as a potential anticancer drug: A review of its molecular targets and anticancer properties. Molecules, Vol. 25. 10.3390/molecules25102278.
10. Zhang, X.W., W. Liu, H.L. Jiang and B. Mao, 2018. Chinese herbal medicine for advanced non-small-cell lung cancer: A systematic review and meta-analysis. Am. J. Chin. Med., 46: 923-952.
11. Nasim, F., B.F. Sabath and G.A. Eapen, 2019. Lung cancer. Med. Clin. North Am., 103: 463-473.
12. Akhurst, T., 2018. Staging of non–small-cell lung cancer. PET Clin., 13: 1-10.
13. Kutob, L. and F. Schneider, 2020. Lung cancer staging. Surg. Pathol. Clin., 13: 57-71.
14. Duma, N., R. Santana-Davila and J.R. Molina, 2019. Non–small cell lung cancer: Epidemiology, screening, diagnosis, and treatment. Mayo Clin. Proc., 94: 1623-1640.
15. Duruisseaux, M. and M. Esteller, 2017. Lung cancer epigenetics: From knowledge to applications. Semin. Cancer Biol., 51: 116-128.
16. Jiang, Y., L.S. Liu, L.P. Shen, J.X. Liu and G.N. Jiang *et al*., 2019. Traditional Chinese medicine treatment as adjuvant therapy in completely resected stage IB-IIIA non–small-cell lung cancer: Study protocol for a multicenter, double-blind, randomized, placebo-controlled trial. Clin. Lung Cancer, 20: E541-E547.
17. Xu, M., C. Wang, M. Zhu, X. Wang, L. Zhang and J. Zhao, 2017. 2,3,5,4-tetrahydroxy diphenylethylene-2-O-glucoside inhibits the adhesion and invasion of A549 human lung cancer cells. Mol. Med. Rep., 16: 8900-8906.
18. Nagasaka, M. and S.M. Gadgeel, 2018. Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. Expert Rev. Anticancer Ther., 18: 63-70.
19. Bamodu, O.A., K.T. Kuo, C.H. Wang, W.C. Huang and A.T.H. Wu *et al*., 2019. *Astragalus polysaccharides* (PG2) enhances the M1 polarization of macrophages, functional maturation of dendritic cells, and T cell-mediated anticancer immune responses in patients with lung cancer. Nutrients, Vol. 11. 10.3390/nu11102264.
20. Jong, C., V.H.M. Deneer, J.C. Kelder, H. Ruven, T.C.G. Egberts and G.J.M. Herder, 2020. Association between serum biomarkers CEA and LDH and response in advanced non-small cell lung cancer patients treated with platinum-based chemotherapy. Thorac. Cancer, 11: 1790-1800.
21. Bello, M.G.D., R.A. Filiberti, A. Alama, A.M. Orengo and M. Mussap *et al*., 2019. The role of CEA, CYFRA21-1 and NSE in monitoring tumor response to Nivolumab in advanced non-small cell lung cancer (NSCLC) patients. J. Transl. Med., Vol. 17. 10.1186/s12967-019-1828-0.

22. Bingula, R., M. Filaire, N. Radosevic-Robin, J.Y. Berthon and A. Bernalier-Donadille *et al*., 2018. Characterisation of gut, lung, and upper airways microbiota in patients with non-small cell lung carcinoma: Study protocol for case-control observational trial. Medicine, Vol. 97. 10.1097/MD.0000000000013676.

23. de Ruysscher, D., C. Faivre-Finn, K. Nackaerts, K. Jordan and J. Arends *et al*., 2020. Recommendation for supportive care in patients receiving concurrent chemotherapy and radiotherapy for lung cancer. Ann. Oncol., 31: 41-49.