

Original Article

Zhenqi Fuzheng combined with chemotherapy for advanced stage lung cancer: a meta analysis

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Abstract: Purpose: To evaluate the outcomes (1 year survival rate, the therapeutic effectiveness and safety) of Zhenqi Fuzheng (ZQFZ) plus chemotherapy compared with chemotherapy alone and clarify its current role for stage II or IV of lung cancer. Methods: Eight studies included 450 patients were analyzed with Revman5.2. Fix models were used to evaluate the outcomes of these studies. Results: Patients receiving ZQFZ plus chemotherapy had significant longer 1-year survival (OR=2.03, 95% CI=1.10-3.73 P=0.02). The clinical curative effective rate (OR=1.44, 95% CI=0.92-2.25, P=0.17) could not be seen significant differences between two groups. The grades of KPS (OR=7.37, 95% CI=3.50-15.52, P<0.00001), Leucopenia (OR=0.33, 95% CI=0.19-0.55, P<0.0001) and Gastrointestinal toxicity reaction (OR=0.57, 95% CI=0.36-0.90, P=0.01) of ZQFZ plus chemotherapy group also displayed more favorable result than chemotherapy alone group. Conclusions: ZQFZ combined with chemotherapy in patients with stage II or IV of lung cancer, to some extent, improved the 1-year survival rate and KPS, associated with lower incidence of Leucopenia and Gastrointestinal toxicity reaction, However, The clinical curative effective rate could not be seen significant differences.

Keywords: Zhenqi Fuzheng, chemotherapy, meta analysis, lung cancer

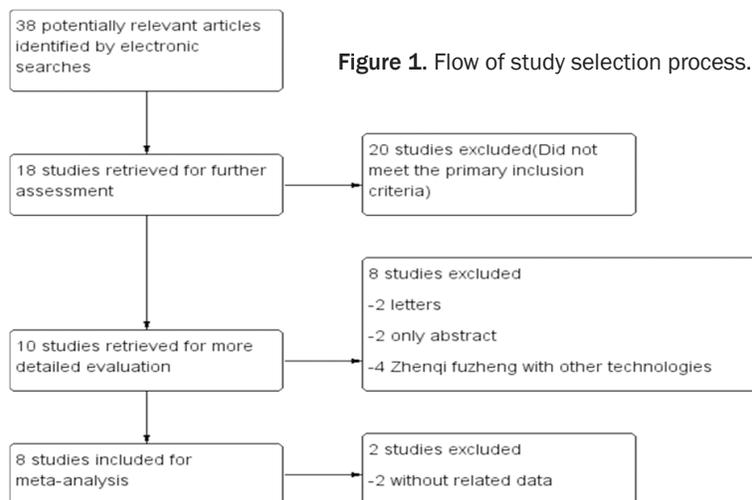
Introduction

At present, the morbidity and mortality of lung cancer have been rising sharply in the world and the incidence rate of lung cancer takes the first place of malignant tumor in China [1]. More than 85% of lung cancer patients were in advanced stage when they obtained final diagnosis, and had lost the chance of surgery treatment [2]. Despite emerging the new diagnosis and treatments, lung cancer prognosis is still poor. The 5-year overall survival for lung cancer with conventional treatments (chemotherapy, radiotherapy and others) is less than 15% in the World [3]. Clinical treatment are mainly containing platinum in the chemotherapy of pulmonary malignant tumor patients and the pulmonary cancer cells reduced sensitivity to platinum may cause tumor recurrence, metastasis, and increase the mortality [4]. So how to improve the treatment effects of pulmonary malignant tumor has caused widespread attention in domestic and foreign scholars.

Chinese medicinal herbs combined with platinum agents in treatment of late stage lung cancer, can significantly improve the clinical symptoms and improve the survival rate, which also suitable for patients without surgical opportunity previously. Chinese herb can be used as auxiliary treatment in patients with pulmonary malignant tumor, safe and feasible, less side effects and good prospect, which is worthy to be popularized in clinical. Clinical studies on early use of Chinese medicinal herbs and chemotherapy are increasing among the different cancers. The Effects of Chinese Medicinal Herbs are mainly on immunologic function in the period of chemotherapy of cancers. Some studies demonstrated that the beneficial effects of traditional Chinese herbs on chemotherapy sensitivity and toxicity of lung cancer. Some studies demonstrated significant antitumor activity against lung cancer with traditional Chinese herbs [5].

Traditional Chinese herbs combined with chemotherapy studied by scholars of our country,

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was approved effective for the treatment of non-small-cell lung cancer, which was better in improving living quality of patients limitation the reduction of WBC(white blood cell) and limitation the side effect of liver and kidneys form toxin effects of chemotherapy [6, 7]. There are many clinical studies of Zhenqi Fuzheng combined with chemotherapy in the treatment of advanced stage lung cancer [8-11]. Recent systematic review has demonstrated that Shenqi fuzheng, an injection concocted from Chinese medicinal herbs, combined with platinum-based chemotherapy for advanced non-small cell lung cancer increase efficacy and reduce toxicity of the patients with advanced stage lung cancer [12].

Zhenqi Fuzheng, an Chinese traditional medicine contains Radix Astragali (Huangqi in Chinese), Fructus Ligustri Lucidi (Nüzhenzi in Chinese), increase the activity of non-specific immunity, improve the anti-tumor effects and attenuate the toxicity of 60 Co [13]. Zhenqi Fuzheng provided a new strategy for the treatment of patients with advanced stage lung cancer in China [14-21]. However, there still lacks comprehensive literature review to evaluate the effects of Zhenqi Fuzheng combined with chemotherapy in the treatment of advanced stage lung cancer with Meta-analysis.

Methods

Literature search strategy

According to the requirements of Cochrane, a thorough literature search was performed among Chinese Digital Hospital Library (www.

chkd.cnki.net) and Chinese Biomedical Literature Disk Database (CBM disk), Wei-Pu database and Wan-Fang database and Chinese scientific journals database. PUBMED, EMBASE. No language restriction was used. The following keywords was used through words linked to lung cancer (lung OR pulmonar AND tumour OR neoplasm OR carcinoma OR cancer), chemotherapy (drug therapy OR chemotherapy), randomised trials (random) and Zhenqi Fuzheng in all fields. It covers past research

and studies and articles from all from January 1999 to 1st January 2016.

Inclusion criteria and study selection

This literature research searched for literatures using the search strategy and screened literatures according to inclusion and excluding criteria. The patient who had been proved through operation and pathology to be suffering from, were analyzed about their imaging indications, and comparative and differentiating studies were included. The review was limited to randomized controlled trials whereas for other groups both randomized controlled studies and nonrandomized, prospective, controlled studies were included. The experimental group was Zhenqi Fuzheng combined with chemotherapy, and the control group was the same as the dose of chemotherapy in the two groups. The outcomes mainly include the short-term effect or the survival rate (1 year survival rate) or toxic and side effects and complications.

Data collection

Two independent researcher surveys and read the relevant information literature, in this based on the summary, to obtain more objective informative material. Two researchers assessed study eligibility and trial quality and extracted the data. One author extracted the data and the two others checked these data and the source from which they were derived. Cochrane system evaluation manual (5.2 Edition) is application for generating documents with content that is e xtracted from the data of applications. Arrangement and Evaluation of the Research

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Table 1. Clinical information of the eligible trails for the meta-analysis

| First author | Nation | Journal | Study type | Sample size | |
|---------------|--------|--|------------|--------------------|----------------|
| | | | | ZQFZ+Chemo | Chemo |
| Zhou T 2005 | China | Chinese journal of pharmcoepidemiology | RCT | 35 (NP) | 35 (NP) |
| Kong YZ 2005 | China | Liaoning journal of traditional chinese medicine | RCT | 32 (GP) | 20 (GP) |
| Zhang MJ 2009 | China | Modern oncology | RCT | 30 (TP) | 28 (TP) |
| Zhang PY 2009 | China | Journal of Chinese Medicine | RCT | 22 (VIP) | 20 (VIP) |
| Wang LT 2010 | China | China Prac Med | Non-RCT | 10 (EP) | 10 (EP) |
| Sun C 2012 | China | Chinese Community Doctors | RCT | 30 (DDP, PTX, NVB) | 28 |
| Chen TJ 2012 | China | Lishizhen medicine and materia medical reasearch | RCT | 42 (GP) | 42 (GP) |
| Liu J 2015 | China | Clinical Misgiagnosis&Mistherapy | RCT | 32 (Gimeracil) | 34 (Gimeracil) |

Table 2. Patient information for the eligible trials

| Study | Treatment regimen | Gender (F/M) | Stage I/II/III/IV | Category Adeno/squamous/Large-cell/Alveolar cell | Treatment line | Median age | Follow-up time (Mon) |
|-------------------|------------------------------------|----------------|------------------------|--|----------------|--------------|----------------------|
| Zhou T 2005 [1] | ZQFZ+NP VS. NP | 46/24 | IIIb-IV | 16/16/1/2 12/20/2/1 | ND | 52 54 | 30 30 |
| Kong YZ 2005 [2] | ZQFZ+GP VS. GP | 23/9 14/6 | 0/0/13/19 0/0/8/12 | 18/11/Unclear/Unclear 12/7/Unclear/Unclear | ≥2nd | 58.6 58.1 | 15 15 |
| Zhang MJ 2009 [3] | ZQFZ+TP VS. TP | 20/10 23/5 | 0/0/24/6 0/0/21/11 | 13/17/0/0 13/15/0/0 | ≥2nd | 56 54 | 24 24 |
| Zhang PY 2009 [4] | ZQFZ+VIP VS. VIP | 14/8 14/6 | Unclear Unclear | SCLC SCLC | 1st | 57 54 | 18 18 |
| Wang LT 2010 [5] | ZQFZ+EP VS. EP | 14/6 | 0/0/8/12 | SCLC SCLC | ≥2nd | Unclear | 36 36 |
| Sun C 2012 [6] | ZQFZ+DDP/PTX/NVB VS. (DDP/PTX/NVB) | 37/21 | IIIb-IV | 26/30/Unclear/Unclear | 1st | 61 | 30 30 |
| Chen TJ 2012 [7] | ZQFZ+GP VS. GP | 24/18 23/19 | 0/0/23/19 0/0/22/20 | Unclear | ≥4th | 54.3 54.6 | 18 18 |
| Liu J 2015 [8] | Experiment: ZQFZ+GP Control: GP | 18/14 19/15 | 0/5/24/3 0/6/25/3 | 11/19/2/0 10/20/4/0 | ≥6th ≥6th | 78.6 79.2 | 24 24 |

Characteristics and the study design (whether the random blind method is used to allocate the hidden, baseline case, etc.) about the literature information. Because high risk of bias of included manuscripts have poor quality, so risk of bias was assessed using the criteria of the Cochrane back review group. Because high risk of bias of included manuscripts have poor quality. The two reviewers discussed the solutions for particular unit about the design method& feasibility of realization and practical application effect.

Measures of curative outcome

Clinical responses such as 1 year overall survival (OS), Objective response rate, KPS score improvement, adverse effects (the Leucopenia and gastrointestinal reaction) and Publication bias were evaluated. Overall survival rates were estimated using the comparing the start time

of treatment to the time of death. The total remission rate (complete response + partial response) in patients receiving the combination therapy and chemotherapy alone was compared. All the adverse effects of patients were consistent with the diagnostic criteria of World Health Organization (WHO).

Quality assessment of trials

Quality Assessment of publications were based on 6 aspects: whether the random allocation was used to form the comparison groups in the trial, whether or not to use the blind method and whether avoiding selective bias (low, unknown and high risk bias).

Statistical analysis

The fix effect model of Meta analysis was performed by using the statistical software Review

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Table 3. Quality assessment of RCT by Cochrane collaboration's tool for assessing risk of bias

| Author | Year | Selection bias | Performance bias | Detection bias | Attrition bias | Reporting bias | Other bias |
|----------|------|----------------|------------------|----------------|----------------|----------------|------------|
| Zhou T | 2005 | Unclear | High | Unclear | Low | High | Low |
| Kong YZ | 2005 | Unclear | High | Unclear | Low | Low | Low |
| Zhang MJ | 2009 | Unclear | High | Unclear | Low | High | Low |
| Zhang PY | 2009 | Unclear | High | Unclear | Low | Low | Low |
| Sun C | 2012 | Unclear | High | Unclear | Low | High | Low |
| Chen TJ | 2012 | Unclear | High | Unclear | Low | Low | Low |
| Liu J | 2015 | Unclear | High | Unclear | Low | Low | Low |

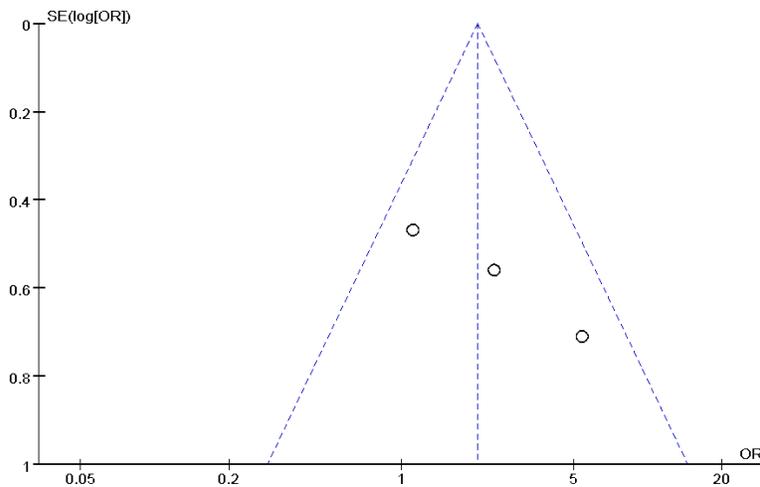


Figure 2. Funnel plot of comparison: 1 OS, outcome: 1.1 1 year OS.

stage lung cancer showed no obvious differences among two groups.

Quality assessment of trials

As shown in **Table 3**, the qualities of articles were assessed and the results suggested high quality of included studies. The table is used to compare the qualities of the 8 publications and get the information of them, and then some measures are taken to eliminate bias. There are no allocations of hidden and blind methods were used in these articles.

Manager (RevMan5.2) on the basis of strict quality evaluation for all the clinical trials reports. Odds ratios and their 95% confidence intervals (CIs) were calculated. Q-test, Heterogeneity and I^2 statistics were compared to test the existence of heterogeneity in meta-analysis in studies.

Results

Selection results

From the clinical trials of Zhenqi Fuzheng combined with chemotherapy for advanced stage lung cancer publications, 8 articles met the criteria of quality evaluation for meta-analysis (**Figure 1**). Detailed characteristics of the studies are presented in **Tables 1** and **2**. The results of all the investigation are conducted in China. Generally, there were 450 patients for treatments: 233 for Zhenqi Fuzheng combined with chemotherapy and 217 for Chemotherapy only. The gender, types and stages of advanced

Publication bias analysis

We performed the publication bias test to evaluate the quality of our Meta analysis. Sensitivity analysis was performed and publication bias was investigated through funnel plots and Egger regression model. Funnel plot was symmetrical in general, and it prompted that no evidence of publication bias in reports on publication bias (**Figure 2**).

Prognosis evaluation: 1 year OS (overall survival)

A total of 3 studies comparing the survival of Zhenqi Fuzheng combined with chemotherapy group and chemotherapy alone group in advanced stage of lung cancer patients. No heterogeneity among them. The rate of 1 year survival in Zhenqi Fuzheng combined chemotherapy group was significantly higher than that in the simple chemotherapy group OR (2.03) and 95% CI (1.01 to 3.73), $P=0.02$ (**Figure 3**).

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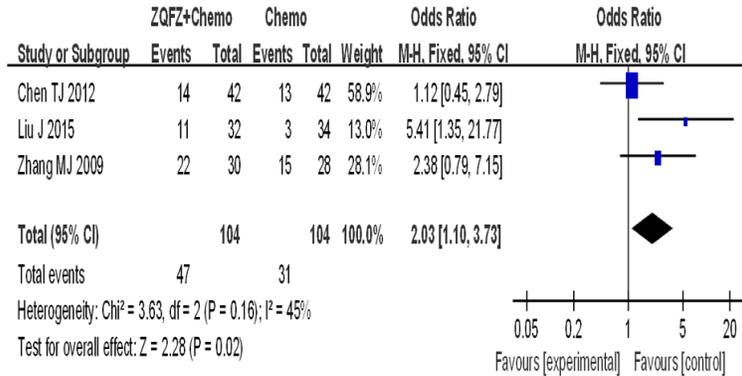


Figure 3. Comparison of 1-year OS between ZQFZ plus Chemo group and Chemo alone group.

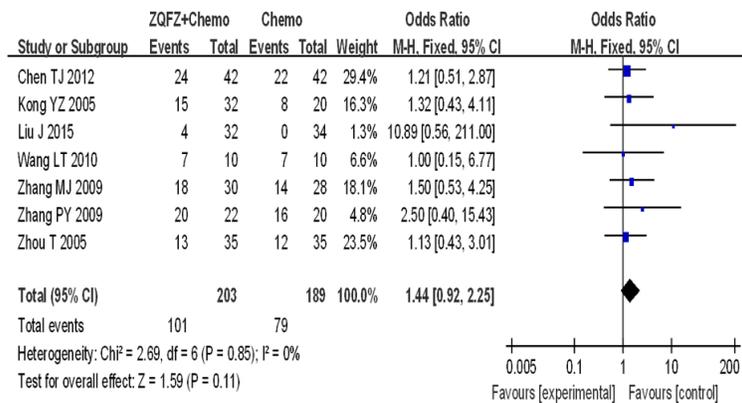


Figure 4. Comparison of overall response between ZQFZ plus Chemo group and Chemo alone group.

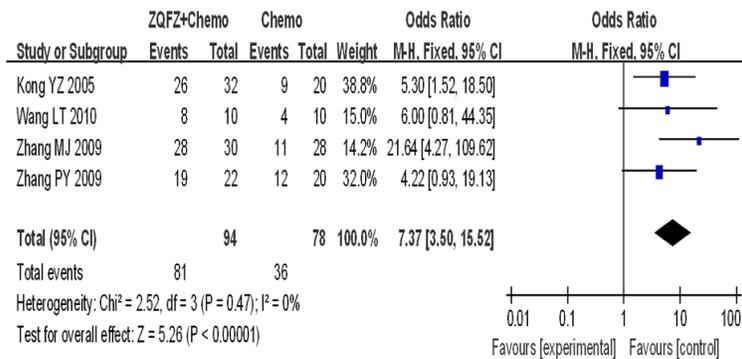


Figure 5. Forest plot for KPS between gastric cancer patients treated with between ZQFZ plus Chemo and Chemo alone group. The random effects model (Mantel-Haenszel method) was used in this analysis.

Clinical curative efficiency

7 studies were included in the analysis of the short-term efficacy Zhenqi Fuzheng combined with chemotherapy and chemotherapy alone in

the treatment of advanced stage lung cancer. But there was no statistically significant difference in the combined OR (1.44) and 95% CI (0.92 to 2.25) between the two group ($P > 0.05$, **Figure 4**).

KPS score evaluation

4 studies were included to compare the quality of life of the Zhenqi Fuzheng combined with chemotherapy and chemotherapy alone in advanced stage lung cancer patients. The data have demonstrated that the improvement of quality of life in patients with Zhenqi Fuzheng combined with chemotherapy group was significantly higher than that of chemotherapy alone group (OR=7.37, 95% CI: 3.50 to 15.52) ($P < 0.00001$) (**Figure 5**).

Safety evaluation of leucopenia

5 studies reported that the incidence of Leucopenia occurred in the two groups. No heterogeneity among the groups, the fixed effect model was used. Compared with chemotherapy alone group, the Zhenqi Fuzheng plus chemotherapy group was less than chemotherapy alone group (OR=0.33, 95% CI: 0.19 to 0.55), $P < 0.0001$ (**Figure 6**).

Gastrointestinal toxicity reaction

6 studies reported that the incidence of Gastrointestinal toxicity reaction. The fix effect model was used for Meta analysis. Zhenqi Fuzheng plus chemotherapy group has less Gastrointestinal toxicity reaction than the chemotherapy group (OR=0.57, (95% CI: 0.36 to 0.90), $P = 0.01$) (**Figure 7**).

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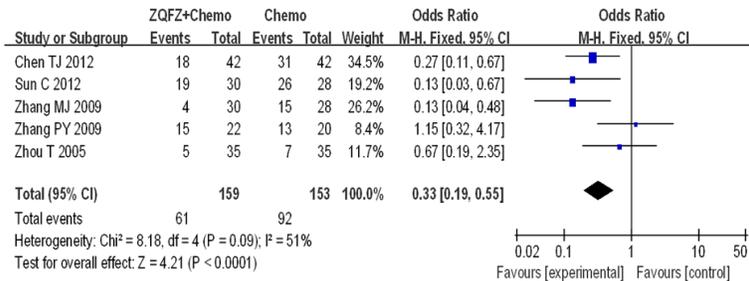


Figure 6. Forest plot for Leucopenia between gastric cancer patients treated with between ZQFZ plus Chemo and Chemo alone group.

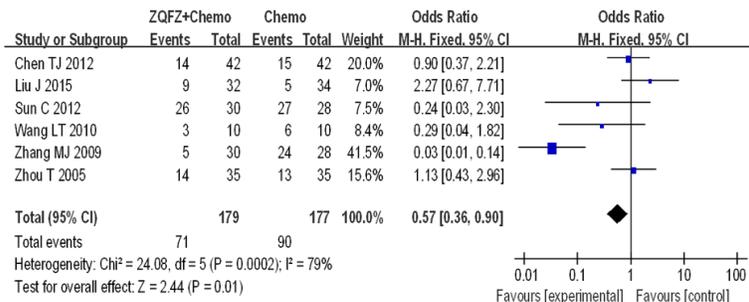


Figure 7. Forest plot for Gastrointestinal toxicity reaction between gastric cancer patients treated with between ZQFZ plus Chemo and Chemo alone group.

Discussion

As for cancer treatment, it is mainly depends on early surgery and radiotherapy as well as chemotherapy, however, either of them has its disadvantage: surgical treatment relies on early diagnosis, and radiotherapy and chemotherapy have too many adverse side effects [22]. The radiotherapy and chemotherapy both could kill the tumor cells, but the treatment could damage the normal tissues meanwhile the patients had serious all over the body adverse reaction [23]. Whether can decrease recurring probability and the occurrence of distant metastasis and improve survival rate, and whether there is an increase of the related adverse reaction in earlier therapy, these are all what we should observe and investigate. Current treatments of chemotherapy and radiotherapy complications are not always successful, highlighting the need to develop new treatment strategies.

The clinical study showed that the Chinese medicinal herbs were simple and effective, especially without general adverse effects as radiotherapy and chemotherapy [24-26]. It is a

good treatment for the old and weak patients with serious systematic diseases. Chinese medicinal herbs combat chemotherapy side effects: If we stick in the process of traditional Chinese medicine combined with, reduce chemotherapy side effects, improve curative effect, suppress or delay tumor growth, improving the quality of life of tumor patients, promoting rehabilitation of cancer patients, reducing relapse and metastasis, extending the role of lifetime.

Traditional Chinese medicine regulates the body's immunity, and has unique advantages in the treatment of this disease [27]. Traditional Chinese medicine is suitable for those who have lost the chance of operation, and are not suitable for chemotherapy

and other treatment of patients, it provides a better therapeutic means [28].

Zhenqi Fuzheng capsule contains Radix Astragalii (Huangqi in Chinese), Fructus Ligustri Lucidi (Nüzhenzi in Chinese), etc. Chinese traditional medical workers were under the Ministry of Health Drug Standards guidance. The experts teams for development and isolation to the traditional Zhenqi Fuzheng capsule was formulated. Investigation of Zhenqi Fuzheng capsule, the chemical constituents mainly include isoflavonoids, triterpene saponins, glycosides, saponin and phenolic acids compounds [29]. An investigation demonstrated that Zhenqi Fuzheng injection increase the activity of non-specific immunity, improve the anti-tumor effects and attenuate the toxicity of ⁶⁰Co [13].

We analyzed 8 studies included 450 patients. The estimated Zhenqi Fuzheng plus chemotherapy for quantitative analysis and compared with chemotherapy alone and clarified its current role for stage II or IV of lung cancer. Patients receiving Zhenqi Fuzheng plus chemotherapy

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had significant longer 1-year survival. Although, no statistically significant difference was observed in the clinical curative efficiency, but the KPS of Zhenqi Fuzheng plus chemotherapy group also displayed more favorable result than chemotherapy alone. At same time, the incidence of leucopenia and gastrointestinal toxicity reaction occurred in Zhenqi Fuzheng plus chemotherapy group are much less than chemotherapy alone.

Zhenqi Fuzheng combined with chemotherapy can improve the overall response efficacy and survival rate of patients, improvement of the quality of life and the reduction of toxic and adverse effect and provide a new strategy for patients with advanced stage lung cancer advanced. Therefore, larger sample and high quality clinical research, which can provide the basis for the treatment of middle and late stage and early stage of treatment for lung cancer are needed for future. The detailed mechanism of how Zhenqi Fuzheng works in chemotherapy is not absolutely clear so far and the quality of included studies were relatively inadequate. Hence, it is necessary to carry out more high quality, large sample, multicenter, prospective, randomized, double blind clinical trials to be further confirmed in the future.

Disclosure of conflict of interest

None.

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