Effectiveness of Traditional Chinese Medicine on chemo-radiotherapy induced leukaemia in patients with lung cancer: a Meta-analysis

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Abstract

OBJECTIVE: To assess the curative effect of Traditional Chinese Medicine (TCM) on leukaemia induced by chemo-radiotherapy in patients with lung cancer.

METHODS: A comprehensive electronic search in Medline, Embase, the Cochrane Library database, China National Knowledge Infrastructure Database (CNKI) and Wanfang Database was conducted up to July 2017. Random-effects model was used to estimate the standardized mean differences (SMDs) with 95% confidence intervals (CIs). Eleven studies with a total of 957 patients were included in this meta-analysis.

RESULTS: The effectiveness in TCM group was higher than control group $[RR = 1.60, 95\% CI (1.38, 1.85), P < 0.000 01]$. Compare with Western Medicine group, the effectiveness has no significant difference $[RR = 0.96, 95\% CI (0.82, 1.12), P = 0.57]$. The ineffective rate in test group was lower than the control group $[RR = 0.30, 95\% CI (0.21, 0.42), P < 0.000 01]$.

CONCLUSION: By meta-regression it was suggested that TCM has curative effect on leukaemia induced by chemo-radiotherapy in patients with lung cancer, but by the influence of number and quality of researches, publication bias, more evidence from high quality studies, and larger cohorts for observational trials are needed.

INTRODUCTION

According to the epidemiological survey, lung cancer is the leading cause of cancer death in China. Most patients with lung cancer have been diagnosed in the terminal stage and lost the operation chance, so chemo radiotherapy-based medical treatment plays an very important role in the treatment of lung cancer. Because chemo radiotherapy not only has effect on cancer cells, but also causes great damage to normal cells, from which a common complication is myelosuppression. Conventional oral Western Medicine, such as colony-stimulating factor for stimulate white blood cell always works slowly, and only keep a short-time effect. During the long-term struggling with disease, Traditional Chinese Medicine has accumulated a wealth of experience, the analysis which reported in 2003 by Li et al. revealed that TCM has significant effect in the
treatment of leukopenia in lung-cancer patients induced by chemo-radiotherapy. Compare with this meta-analysis, our research exactly defined the outcome 'remarkable effect', 'effective', 'invalid', the study method and inclusion criteria also is more preciseness.

METHODS

Inclusion criteria
Study type: all prospective clinical RCTs were included of TCM treatment of leukopenia induced by chemo-radiotherapy in patients with lung cancer. Regardless of whether the implementation of blinding, allocation concealment or the report on drop out and lost of follow up, the text is limited to Chinese/English. Subjects: all cases were lung cancer patients who had been diagnosed as leukopenia induced by chemo-radiotherapy; age, gender, race and area is not limited. Exclusion: Blood system Malignant tumor.

Intervention measurement
Test group: (a) The treatment was guided by Traditional Chinese Medicine (TCM) theory included single herbs, TCM compound, acupuncture-moxibustion and other treatment; (b) Chinese patent medicine; (c) Excluded ethnic medicine.

Control group: given western conventional leucocyte-generate medicine (leucogen, betyl alcohol, amino-polypeptide, vitamin B, vitamin C, etc.) or placebo, or blank control.
The dose of test group and the control group is unlimited, the course of the treatment is same.

Outcome indicators of the improved clinical symptoms and the number of peripheral blood leucocyte.
(a) remarkably effect: the clinical symptoms disappeared, the number of peripheral leucocyte $\geq 4 \times 10^9$ / L. (b) effective: clinical symptoms improved, peripheral blood leucocyte number $< 4 \times 10^9$ / L, compared with the prior treatment, it increased by $0.5-1.0 \times 10^9$ / L or peripheral blood leucocyte count $\geq 3.5 \times 10^9$ / L. (c) invalid: no improvement in clinical symptoms, peripheral blood leucocyte number was no significant increase, or peripheral blood leucocyte count $\leq 3.4 \times 10^9$ / L.

Exclusion criteria
Only abstracts without full text, repeated publication or incomplete data articles.

Search strategy
A comprehensive electronic search in Medline, Embase, the Cochrane Library database, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI), Wanfang Database was conducted from inception to July 2017, using both free words and index terms specific to each search platform. The search strategies were based on combinations of the keywords: 'Traditional Chinese Medicine, Chinese herbs, lung neoplasm, pulmonary neoplasm, lung cancer, pulmonary cancer, adenocarcinoma, squamous cell carcinomas, leukopenia'. The electronic investigation was supplemented with a manual search of references of all articles retrieved. The latest searches were undertaken to 1 July 2017. Language limited to English and Chinese. Two reviewers independently searched the electronic databases, and screened the titles, abstracts, and full-text after excluding duplicated studies. Any discrepancy in the screening process was resolved by consultation of the group. Take PubMed as an example, its specific search strategy is shown bellow.
1#Medicine, Chinese Traditional Chinese OR Drug / therapeutic use
2#Lung Neoplasms OR Pulmonary Neoplasm OR lung cancer OR Pulmonary Cancer OR Adenocarcinoma OR Carcinoma, Squamous Cell / diagnosis
3#Leukopenia /drug therapy

Quality score assessment
Quality evaluation of included studies was conducted according to the Newcastle-Ottawa Scale with minor modification. The quality assessment criteria used in the study were: (a) whether the diagnosis of the leukemia was caused by chemo radiotherapy in lung cancer with independent validation; (b) whether the involved cases were representative of population; (c) whether the controls enrolled were from the same community; (d) whether the controls were described to have no history of disease; (e) whether the cases and controls were matched for age or BMI; (f) whether the cases and controls were matched for additional factor, such as drinking or smoking status; (g) whether the sample size was $> 50$. For each criterion a score of 0 or 1 was assigned according to whether the criterion was satisfactorily fulfilled. According to the quality score assessment, the distribution of the scores was between 0 and 6. Studies with score of 5 or above are classified as high quality studies. Others are categorized as low quality studies.

Data extraction
Two of the authors independently extracted the data from the included studies. The general characteristics of the study were extracted using a standardized data extraction form. The general characteristics, such as name of the first author, year of publication, diagnostic criteria, control group and primary outcomes were listed. If the two investigators could not reach an agreement, the dispute was resolved by a third reviewer.

Statistical analysis
Heterogeneity across studies was quantified using the $Q$-statistic and inconsistency index ($I^2$). If $P < 0.10$, the heterogeneity was considered as statistically significant. If $I^2 > 50\%$, it was considered as large heteroge-
neity; if $I^2 = 25\%-50\%$, as moderate heterogeneity and if $I^2 < 25\%$, as absent of heterogeneity. In case of large heterogeneity ($I^2 > 50\%$), random-effects model was applied since it was usually more conservative. Otherwise, a fixed-effects model was used. When the heterogeneity is obviously different from the methodological quality of the included research, the stability of the results can be evaluated by sensitivity analysis, and the potential publication bias of the article is analyzed by using the funnel plot.

**DATA SEARCH OUTCOMES**

Based on our search strategy through comprehensive searching, A total of 11 articles met the inclusion criteria following the screening process and were included in quantitative synthesis. Retrieving articles were assigned to studies conducted between 2002 and 2017. The basic characteristics of the included study in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Cases</th>
<th>Control</th>
<th>Intervention measure</th>
<th>Course</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liu AQ et al</td>
<td>2015</td>
<td>China</td>
<td>30</td>
<td>30</td>
<td>Bazhen decoction</td>
<td>2 weeks</td>
<td>①②</td>
</tr>
<tr>
<td>Cai ZQ et al</td>
<td>2012</td>
<td>China</td>
<td>30</td>
<td>30</td>
<td>Modified Bazhen decoction</td>
<td>3 weeks</td>
<td>①②</td>
</tr>
<tr>
<td>Hao HJ et al</td>
<td>2015</td>
<td>China</td>
<td>30</td>
<td>30</td>
<td>Sanhuang Sanxian decoction</td>
<td>12 days</td>
<td>①②</td>
</tr>
<tr>
<td>Xian HM et al</td>
<td>2008</td>
<td>China</td>
<td>30</td>
<td>30</td>
<td>Modified Bazhen decoction</td>
<td>21 days</td>
<td>①②</td>
</tr>
<tr>
<td>Zhou XJ et al</td>
<td>2013</td>
<td>China</td>
<td>41</td>
<td>40</td>
<td>Kedeli oral liquid</td>
<td>Blank control</td>
<td>①②</td>
</tr>
<tr>
<td>Xiang JC et al</td>
<td>2013</td>
<td>China</td>
<td>120</td>
<td>120</td>
<td>Qishu decoction</td>
<td>10 days</td>
<td>①②</td>
</tr>
<tr>
<td>Sun FC et al</td>
<td>2002</td>
<td>China</td>
<td>32</td>
<td>28</td>
<td>Shengbai granule</td>
<td>Placebo</td>
<td>①②</td>
</tr>
<tr>
<td>Chen C et al</td>
<td>2013</td>
<td>China</td>
<td>58</td>
<td>50</td>
<td>Shengbai oral liquid</td>
<td>Leucogen tablets</td>
<td>①②</td>
</tr>
<tr>
<td>Liu SJ et al</td>
<td>2015</td>
<td>China</td>
<td>60</td>
<td>60</td>
<td>Generate marrow Zusanli decoction + Chinese medicine</td>
<td>3 weeks</td>
<td>①②</td>
</tr>
<tr>
<td>Wang M et al</td>
<td>2016</td>
<td>China</td>
<td>24</td>
<td>24</td>
<td>Blank control</td>
<td>28 days</td>
<td>①②</td>
</tr>
<tr>
<td>Ding QG et al</td>
<td>2017</td>
<td>China</td>
<td>30</td>
<td>30</td>
<td>Blank control</td>
<td>21 days</td>
<td>①②</td>
</tr>
</tbody>
</table>

Notes: ① markedly: the clinical symptoms disappeared, the number of peripheral blood leukocyte $\geq 4 \times 10^9$/L. ② effective: clinical symptoms improved, peripheral blood leukocyte number $< 4 \times 10^9$/L, compared with prior treatment, it increased by $0.5\sim1.0 \times 10^9$/L or peripheral blood leukocyte count $\geq 3.5 \times 10^9$/L. ③ invalid: no improvement in clinical symptoms, peripheral blood leukocyte number was no significant increase, or peripheral blood leukocyte count $\leq 3.4 \times 10^9$/L.

**RESULTS**

Of the 157 search outcomes, 108 were excluded by screening their titles and abstracts, and 49 remained for full-text review to determine eligibility. A total of 485 lung cancer patients who had leukaemia after...
A total of 11 studies \((n=957)\) reported significant efficiency. The results of fixed effect model (Meta-analysis) showed that the markedly effective rate of the test group was higher compared to that of the control group \(\text{RR} = 1.60, 95\% \text{ CI} (1.38, 1.85), P < 0.000\,01\), the difference was statistically significant (Figure 2).

A total of 11 studies \((n=957)\) reported inefficiencies. The results of fixed effect model (Meta-analysis) showed that the ineffective rate of the two groups is no significantly different \(\text{RR} = 0.96, 95\% \text{ CI} (0.82, 1.12), P = 0.57\) (Figure 3). The difference was not statistically significant \((P > 0.05)\).

A total of 11 studies \((n=957)\) reported inefficiencies. The results of fixed effect model (Meta-analysis) showed that the ineffective rate of the test group was lower compared to that of the control group \(\text{RR} = 0.30, 95\% \text{ CI} (0.21, 0.42), P < 0.000\,01\), the difference was statistically significant (Figure 4).

Both Figures 5 and 6 show an asymmetric scatter plot, suggesting that the inclusion of the study may exist publication bias.

### DISCUSSION

Secondary leukemia is a common late complication after exposure to cancer therapies such as chemotherapy and radiotherapy. A number of clinical studies\(^{5-11}\) reported that dialectical treatment of TCM can improve the clinical symptoms and life quality of lung cancer patients, as well as reduce myelosuppression and other side effect, so as to increase the patient’s tolerance to chemo radiotherapy.

In this study, Cochrane systematic evaluation to the curative effect of dialectical treatment of TCM treatment of leukaemia induced by chemo-radiotherapy in patients with lung cancer has practical significance to clinical work. Meta analysis showed that the TCM dialectical treatment of chemo-radiotherapy induced leukaemia has a significant effect. The markedly effective rate of the test group was higher than that of the control group, the inefficiency was lower than that of the control group, and the difference was statistically significant; and there was no significant difference in efficiency of the two groups. We can see from the funnel plot, the inclusion of the literature may exist publication bias.

The limitations of this study: (a) The quality of the research methodology in 11 studies is not high, although all studies refer to the words "random", only four studies describe the specific stochastic method as "random number table", all studies allocation concealment is unclear, all studies did not mention blindness. (b) This study included only published literature, not included the unpublished gray literature, which may have some influence on the results of Meta-analysis. (c) The in-
Figure 1 Flow diagram of the literature selection

Figure 2 Meta-analysis of remarkably effect between Chinese medicine group and control group

Figure 3 Meta-analysis of effective between Chinese medicine group and control group
cluded studies do not describe the estimation of the sample size in detail, resulting in the test performance reduced. (d) Funnel plot analysis suggests that there may be publication bias, expect more high-quality clinical RCTs to carry out. (e) Most of the included studies reported fewer adverse events, so they could not be evaluated for safety. (f) Included articles didn’t describe the details of the amount of WBC before and after treatment, so that meta analysis could not assess the changes after therapy.

In conclusion, the effectiveness of TCM treatment of chemo-radiotherapy induced leukaemia is significant, but due to the limitations of literature quality, sample size and research design, the above conclusions still need more large high-quality samples of RCT to verification.

REFERENCES


