

Original Research Article

Meta-analysis of effectiveness of traditional Chinese medicine or its combination with Western medicine in the treatment of triple negative breast cancer

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Abstract

Purpose: To assess the efficacy and side effects of Traditional Chinese Medicine (TCM) in the management of triple negative breast cancer (TNBC).

Methods: Full text data on randomized controlled trial (RCT) of TNBC treated with TCM or its combination with Western Medicine (WM) were retrieved from the Chinese biomedical literature database, Chinese periodicals, Chinese Science-Technology periodicals and VP and PubMed. The qualities of the RCTs were evaluated. Revman 5.3 was used to conduct the meta-analysis.

Results: A total of 16 RCTs involving 1186 patients were included. Analysis of these RCTs showed significant differences in total effectiveness between WM and TCM or combination of TCM with WM {(OR = 2.63, 95 % CI = 1.37, 5.03), test of the combined effect (Z = 2.91, p < 0.005)}.

Conclusion: The results show that TCM is effective in the treatment TNBC.

Keywords: Triple negative breast cancer, Chinese medicine therapy, Meta-analysis, Randomized controlled trial

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INTRODUCTION

Negative-expressions of human-epidermal-growth-factor-receptor-2 (Her-2), progesterone receptor (PR), and estrogen receptor (ER) are characteristic features of TNBC, a malignant tumor with strong invasiveness and poor prognosis [1]. The current treatments for TNBC involve the use of chemotherapy, radiation therapy, molecular targeted therapy and Chinese medicine [2]. The prognosis of WM treatment is

worse for TNBC than general breast cancer, due to more severe adverse reactions. In contrast, TCM achieves better results which have been recognized by many scholars. Thus, studies on TCM and integration of TCM and WM for the treatment of TNBC are increasing year after year. However, the universality of the safety and efficacy of TCM have not been investigated. Furthermore, it is necessary to systematically evaluate existing evidence with respect to its safety and universality using quantitative indicators. The current study focused on

systematic analysis of effectiveness of only TCM or in combination with WM to treat TNBC.

METHODS

Participants

These included patients were diagnosed with triple-negative breast cancer by postoperative pathological diagnosis, imaging examination and hormone receptor examination and randomized controlled trials (RCTs) involving treatment with TCM or integration of TCM and WM, blinded or un-blinded.

The Ethical Committee of Department of General Surgery, Jiashan First People's Hospital, Jiashan, Zhejiang, China, approved this study (approval no. 201811725), which was conducted based on the Helsinki Declaration [3].

Inclusion criteria

Diagnostic criteria

These included postoperative pathological examination resulting in diagnosis of breast cancer, and immunohistochemistry showing negative expressions of ER, PR and HER-2.

Intervention

Studies involving treatment with TCM or combination of TCM and WM in which the TCM was given through oral administration, external application and emotional therapy, and (b) studies in which the control group used WM treatment methods such as surgery, WM, and radiotherapy, and combination treatment studies involving use of both TCM and strategies, were included.

Study indices

Studies in which clinical remission was evaluated according to WHO evaluation criteria; studies in which total effectiveness was evaluated as the sum of complete responses and partial responses, with secondary observation indicators such as quality of life, immune indicators and survival rates, were included.

Exclusion criteria

The excluded studies were: non-RCT literature, randomized controlled trials involving different Chinese medicine or integrated TCM and WM treatment regimens in the control-group and the treatment-group, non-clinical studies, studies without clinical observation, studies involving

animal experiments, reviews, and clinical studies without statistical analysis.

Literature search

The search database included China Journal Full-text Database "China National Knowledge Internet (CNKI)", Chinese Science and Technology Periodical Database (VIP), China Biomedical Literature Database (CBM), PubMed and Wanfang. The search terms included: TNBC, TCM, WM, Chinese Herbal Drug, etc.

Data extraction and quality assessment

Cochrane System Evaluator's Handbook (version 5.1.0) was combined with the Jadad 3 item 5-point method for evaluation of the qualities of the included researches [4]. The scoring-criteria was like the following: double-blinded and appropriate double-blinded method description were scored one point; description of appropriate randomized method was scored one point; and description of follow-up and withdrawal status was scored one point. Publication quality was scored low (0 to 2 points), or high (3 to 5 points). Two evaluators worked independently to evaluate the publications in line with the above criteria. If there are disagreements between the two assessors, they were resolved through a third party.

Statistical analysis

RevMan 5.3 statistical software (Cochrane) was used. Heterogeneity test was carried out with χ^2 -test ($\alpha = 0.01$, $I^2 = 50\%$). Heterogeneity was indicated when $p \geq 0.1$ and $I^2 \leq 50\%$, and the fixed effect model was used for meta-analysis. On the other hand, if $I^2 \geq 50\%$ and $p < 0.1$, the random-effect-model (REM) would be adopted. The representation of the count data was based on an estimate of relative risk (OR) and its 95% CI.

RESULTS

The search results were screened from 1193 relevant studies according to inclusion criteria and exclusion criteria, and 16 studies were finally included. These involved a total of 1186 patients, as shown in Table 1.

Meta-analysis results

Total effectiveness referred to the sum of partial remission and complete remission. Eight studies (542 patients) reported remission of TNBC treated with TCM or combination of traditional Chinese and WM, relative to WM. The results of meta-analysis revealed that heterogeneity test p

Table 1: Basic characteristics of, and Jadad scores for the research works

Author	Stochastic method	Blind method	Exit lost visit	Jadad score	Intervention (treatment/control)	Total number of cases (trial/control)	Year of publication
Xu Chuan [5]	Random	Not stated	No loss to follow-up	2 points	Radiotherapy and Chemotherapy+Ruyanning Prescription/Radiotherapy and Chemotherapy	60(30/30)	2015
Chen Yu [6]	Random number method	Not stated	No loss to follow-up	3 points	Traditional Chinese Medicine Treatment/Western Medicine Treatment	98(50/48)	2015
Zhang Qiang [7]	Random number method	Not stated	Not stated	2 points	Shenqi Fuzheng Liquid+/Western Medicine Treatment	100(50/50)	2013
Lu Yuanzhong [8]	random	Not stated	No loss to follow-up	2 points	Tribulus terrestris Bushen Mixture/Chemotherapy	100(50/50)	2010
Zhu Jing [9]	Random	Not stated	No loss to follow-up	2 points	Xiaoyao Sanjiao+Capecitabine/Capecitabine	56(32/24)	2014
Xiao Li [10]	Random	Not stated	Not stated	1 point	Shenyi Capsule+Capecitabine/Capecitabine	30(15/15)	2014
Lv Xiaoai [11]	Random number method	Not stated	Not stated	2 points	Sanye Qingsan+Chemotherapy/Chemotherapy	107(55/52)	2014
Cui Honghai [12]	random	Not stated	Not stated	1 points	Shugan Jianpi Jiedu Powder+Chemotherapy/Chemotherapy	60(30/30)	2015
Wang Zhiguang [13]	Random number method	Not stated	1 case lost to follow up	3 points	Shugan Jianpi Yishen Traditional Chinese Medicine+Chemotherapy/Chemotherapy	60(30/30)	2015
Ren Xiaoyin [14]	random	Not stated	Not stated	1 point	Traditional Chinese Medicine for Soothing Liver, Strengthening Spleen and Benefiting Kidney+GT Chemotherapy	50(25/25)	2015
Tang Rui [15]	Random	Not stated	No loss to follow-up	2 points	Yiqi Rehabilitation Prescription+Western Medicine Treatment/Western Medicine Treatment Traditional Chinese Medicine Emotional Therapy + Western Medicine Therapy/Western Medicine Therapy	59(30/29)	2016
Li Yang [16]	Random number method	Not stated	Not stated	2 points	Refining and Kidney-tonifying Prescription+Chemotherapy/Chemotherapy	90(45/45)	2015
Zheng Guilan [17]	Random number method	Not stated	2 cases of withdrawal	3 points	Traditional Chinese Medicine+Western Medicine Treatment/Western Medicine Treatment Shuijin Capsule+Western Medicine Treatment/Western Medicine Treatment Traditional Chinese Medicine Compound Formula+Chemotherapy/Chemotherapy	60(30/30)	2010
Chen Hai [18]	Random number method	Not stated	No loss to follow-up	3 points	Traditional Chinese Medicine+Western Medicine Treatment/Western Medicine Treatment Shuijin Capsule+Western Medicine Treatment/Western Medicine Treatment Traditional Chinese Medicine Compound Formula+Chemotherapy/Chemotherapy	98(50/48)	2014
Huang Xiying [19]	Random number method	Not stated	Not stated	2 points	Traditional Chinese Medicine Compound Formula+Chemotherapy/Chemotherapy	60(30/30)	2011
Chen Zhijia [20]	Random number method	Not stated	Not stated	2 points	Traditional Chinese Medicine Compound Formula+Chemotherapy/Chemotherapy	98(50/48)	2015

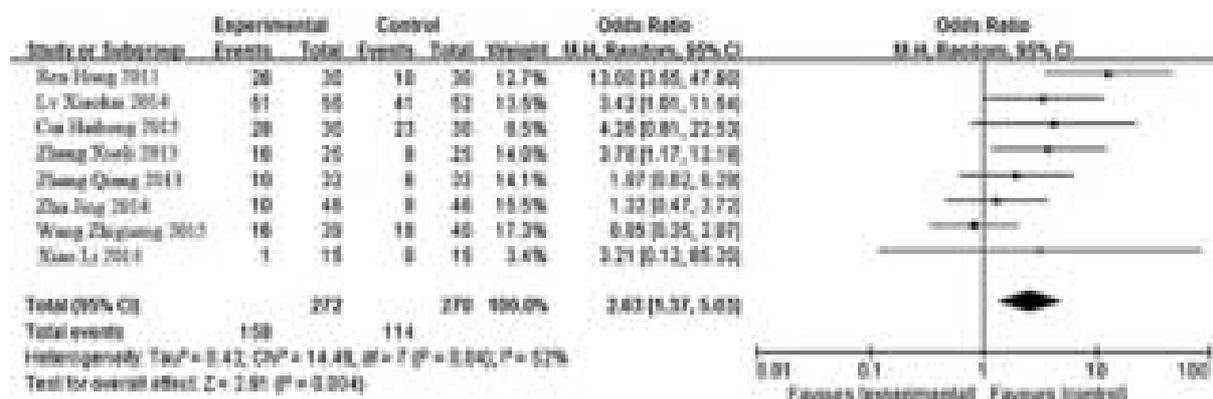


Figure 1: Total effectiveness in TCM, integrated TCM and WM, and WM groups

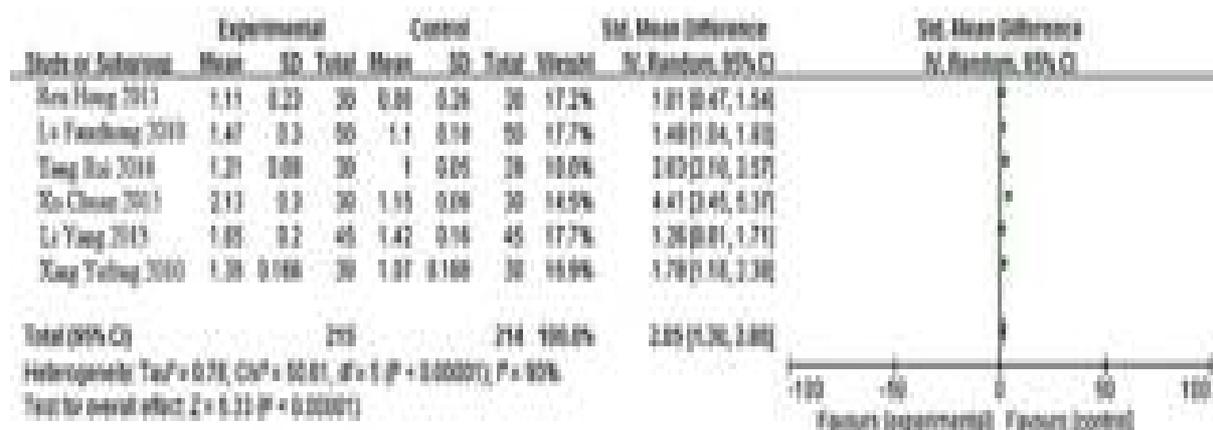


Figure 2: CD4/CD8 in the treatment of TNBC with TCM or TCM-WM combination, and WM

was 0.004 (i.e. below 0.1). Thus, REM was adopted. The combined effect OR value was 2.63, with 95 % CI = 1.37, 5.03. The combined effect Z value was 2.91 ($p < 0.005$), indicating a significant difference between the experimental-group and the control-group. The curative-effects in experimental-group were better than those in control-group. These results are shown in Figure 1.

Immune function

Six of the 16 studies used CD4/CD8 T cell ratio as the effect index in 429 patients (215 cases received TCM or integrated TCM and WMs, while 214 cases received WM in the control-group). The heterogeneity test $p < 0.00001$. Thus, REM was adopted, and the combined effect-size was SMD (95 % CI = 1.30, 2.80; Z = 5.33; $p < 0.00001$), indicating that the CD4/CD8 ratios in TCM or integrated TCM and WM group were higher than those in WM control-group after treatment (Figure 2).

Quality of life

Six out of the 16 studies described evaluation of

the quality of life, and the KPS life status score was used as the observation index. However, one comparison was reflected in the form of mean variance, so it was not included. Totally, 339 patients were enrolled finally, comprising 170 treated with TCM or integrated TCM and WM, and 169 patients in the control group treated with WM. In heterogeneity-test, $p < 0.00001$, thus REM was used. Combined OR value is 3.66; 95 % CI = 2.07, 6.48; Z = 4.45; $p < 0.00001$, indicating that the life qualities associated with TCM or integrated TCM and WMs were better than those seen in WM control group. These results are shown in Figure 3.

Survival rate

Four out of the 16 studies reported survival rate, and involved a total of 394 patients, 200 of whom were treated with TCM or TCM-WM combinations, while 194 patients received WM (control group). In heterogeneity-test, $p < 0.0001$. Thus, the REM was used. The pulled OR = 6.89; 95 % CI = 2.81, 16.87; the combined effect test $p = 0.00014.22$, indicating that the survival rate of patients treated with TCM or TCM plus WM was

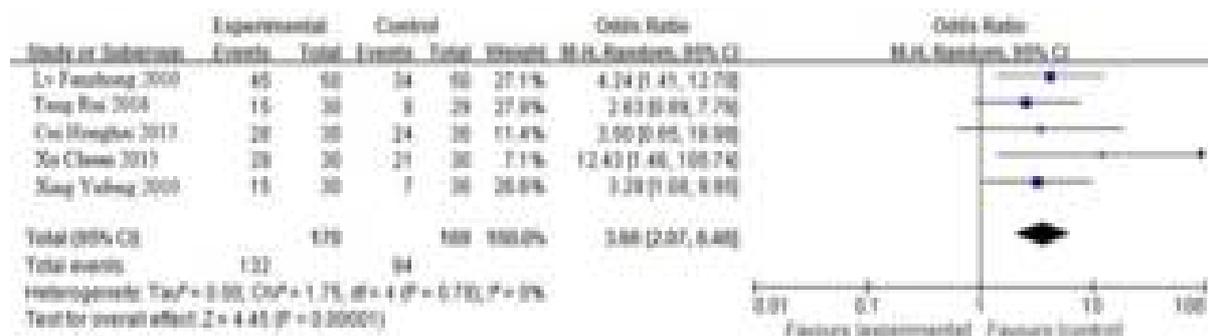


Figure 3: Quality of life in TNBC patients treated with TCM or Chinese-Western combination, and WM

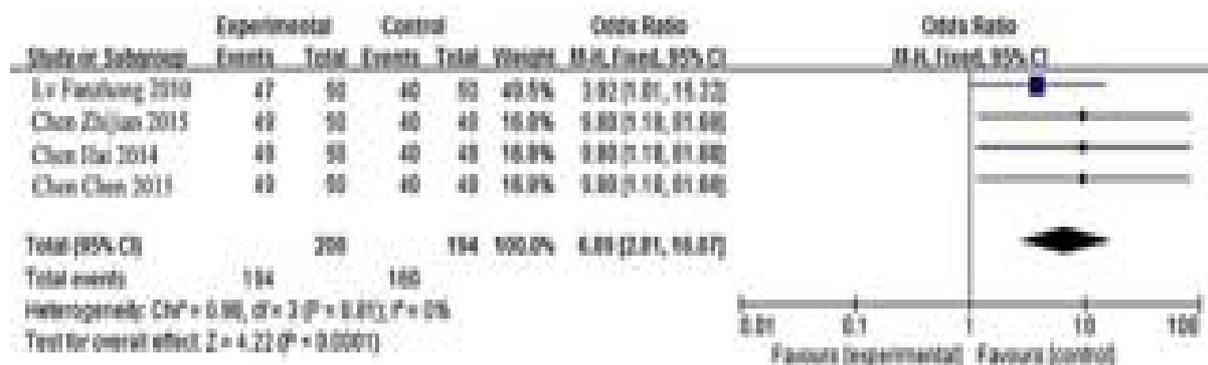


Figure 4: Survival rate of TNBC patients treated with TCM or TCM plus WM, and WM

better than that of those treated with WM (Figure 4).

Publication bias

Meta-analysis of selected literature may be subject to publication bias to a large extent. In practice, the existence or absence of publication bias can often be judged by the use of the funnel plot. The OR value of the comprehensive effect in the included study is the abscissa and the reciprocal of the OR standard error is the ordinate. In this study, the funnel chart was drawn using statistical analysis software (Figure 5). It can be seen that there was no obvious publication bias.

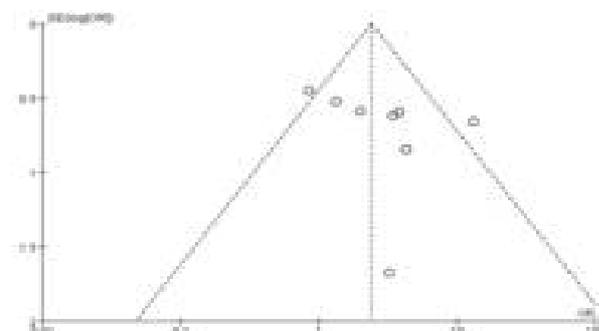


Figure 5: Funnel plot for publication bias

DISCUSSION

TNBC is with a high recurrence rate, easy metastases and poor prognosis [21,22]. Although a large number of clinical trials have been conducted, no targeted treatment regimens have been identified. Triple-negative breast cancer is categorized in TCM as “Shijie” and “lactstone”. TCM is usually applied according to the etiology and pathogenesis of TNBC. Individualized treatment plans are used for the specific conditions of each patient. Moreover, Chinese medicine is used in combination with WM to treat TNBC. In the present study, the meta-analysis included 16 articles involving a total of 1186 subjects. After analyzing the effect indicators such as total effectiveness, CD4/CD8T ratio, quality of life and survival rate, it was found that the difference is obvious between the group with TCM/integrated TCM and WM, and the group given WM only. Moreover, no serious adverse reactions were associated with combined treatment with TCM and WM, or TCM alone. This indicates that TCM or TCM plus WM has certain advantages over WM to treat TNBC. These advantages include reduction in the side effects of radiotherapy and chemotherapy, improvement in the quality of life of patients, recurrence of anti-tumor metastasis, and higher survival rate. Thus, the combined treatment is a new and beneficial strategy for clinical treatment of TNBC.

Heterogeneity test showed that there was high heterogeneity between the studies. This may be related to the intervention, experimental design and quality of the studies used. Most of the literature mentioned only random grouping, but did not use blinding method. This may also be responsible for observed heterogeneity. The study did not carry out further analysis to identify the sources of heterogeneity, thus REM was adopted. Low publication bias between the studies improved the reliability of the analysis results.

CONCLUSION

The results of the analyses carried out in this study show that TCM is effective in the treatment of TNBC. However, the efficacy of TCM or TCM plus WM for treating TNBC should be subjected to further studies. The present investigation reveals that most of the included articles had low Jadad scores, and the method of random grouping was not specifically described. Moreover, blinding was not specified and the losses to follow-up were not indicated in many instances. These lapses made it difficult to judge rationality of the experimental design and results. In addition, most of the included literature did not classify and reflect syndrome differentiation and treatment in Chinese medicine. Therefore, more large-scale, multi-center, completely randomized controlled clinical trials are needed to demonstrate the safety and effectiveness of TCM to treat TNBC.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the author(s) named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors, all authors read and approved the manuscript for publication. He Fan and Zeng Jiayao conceived and designed the study, Wang Yukun, Yao Chang, He Fan collected and analysed the data, Wang Yukun wrote the manuscript. He Fan and Zeng Jiayao are co-corresponding authors.

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