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

Wang Yukun¹, Yao Chang², He Fan³, Zeng Jiayao¹*

¹Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Guangxi University of Traditional Chinese Medicine, Nanning, Guangxi 530023, ²Department of Breast Surgery, Jiangsu Province Traditional Chinese Medicine Hospital, Nanjing, Jiangsu 210029, ³Department of General Surgery, Jiashan First People’s Hospital, Jiashan, Zhejiang 314100, China

*For correspondence: Email: nl1196@163.com

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 $\chi^2$-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    | Sanjiao+Capecitabine/Capscitabine Shenyi Sanye                                                | 56(32/24)                             | 2014               |
| Xiao Li [10]    | Random             | Not stated   | Not stated                        | 1 point     | Capsule+Capecitabine/Capscitabine Shenyi Sanye                                                | 30(15/15)                             | 2014               |
| Lv Xiaoi [11]   | Random number method | Not stated | Not stated                        | 2 points    | Qingsan+Chemotherapy/Chemotherapy                                                              | 107(55/52)                            | 2014               |
| Cui Honghai [12] | random            | Not stated   | Not stated                        | 1 point     | Shugan Jianpi Jiedu Powder+Chemotherapy/Chemotherapy                                           | 60(30/30)                             | 2015               |
| Wang Zhiguan [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          | 59(30/29)                             | 2016               |
| Li Yang [16]    | Random number method | Not stated | Not stated                        | 2 points    | Medicine Emotional Therapy + Western Medicine Therapy                                           | 90(45/45)                             | 2015               |
| Zheng Guilan [17] | Random number method | Not stated | 2 cases of withdrawal             | 3 points    | Refining and Kidney-tonifying Prescription+Chemotherapy/Chemotherapy Traditional Chinese Medicine+Chemotherapy | 60(30/30)                             | 2010               |
| Chen Hai [18]   | Random number method | Not stated | No loss to follow-up              | 3 points    | Medicine+Western Medicine Treatment/Western Medicine Treatment                                | 98(50/48)                             | 2014               |
| Huang Xiyang [19] | Random number method | Not stated | Not stated                        | 2 points    | Shuixin Capsule+Western Medicine Treatment/Western Medicine Treatment                           | 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               |
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 WM, 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 $p = 0.0014.22$, 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.

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 regimen has 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.

REFERENCES

1. Costa R, Shah AN, Santa-Maria CA, Cruz MR, Mahalingam D, Carneiro BA, Chae YK, Cristofanilli M, Gradishar WJ, Giles FJ. Targeting Epidermal Growth Factor Receptor in triple negative breast cancer: New discoveries and practical insights for drug development. Cancer Treat Rev 2017; 53: 111-119.
2. Li KX, Zhou M, Qiang Q, Sun XY, Wang XM. Research progress of triple negative breast cancer and treatment of traditional Chinese medicine. Hubei J Tradit Chin Med 2015; (03): 76-78.
3. World Health Organization. Declaration of Helsinki. Br Med J 1966; 313(7070): 1448-1449.
4. Zhao J, Du JH, Wang GL, Gao YJ, Yi QS, Wang BY. Meta-analysis of randomized controlled trials of traditional Chinese medicine in the treatment of essential hypertension. Chin J Tradit Chin Med 2018; (3): 922-926.
5. Xu C, Tong X, Yu XW, Li SL, Li M. Clinical study of Ruyan Ningfang in the treatment of triple negative breast cancer. Gansu Med J 2015; 34(11): 821-822.
6. Chen W, Liu H. Study on the Effect of Syndrome Differentiation of Traditional Chinese Medicine on Survival Rate of Patients with Sanyin Breast Cancer [J]. Shizheng Guo Yi Guo Yao, 2015(01): 156-157.
7. Zhang Q, Cai JB, Chen X, Shi WM, Yang LJ, Zhou J. Treatment of 32 cases of advanced triple-negative breast cancer with Shenqi Fuzheng injection combined with chemotherapy. Chin Pharm 2013; 16(12): 1866-1867.
8. Lv YZ, Kong QZ. Clinical study on the treatment of triple-negative breast cancer after operation with Qibu Shen Mixture. Hubei J Tradit Chin Med 2010; 32(6): 16-17.
9. Zhu J. Clinical study of Pitabine maintenance therapy combined with Xiaoayao Powder in the treatment of advanced triple-negative breast cancer. Hubei Univ Tradit Chin Med 2014; 24: 123-155.
10. Xiao L. Clinical efficacy of ginsenoside Rg3 combined with capcicatine in the treatment of advanced triple-negative breast cancer. Hebei Med 2015; (16): 2445-2447.
11. Lv XT, Wang W, Chen JB, Ye J. Pathological complete response rate of Sanye Qingsanjie anticancer prescription in patients with triple negative breast cancer treated with neoadjuvant chemotherapy. J Tradit Chin Med 2014; 55(23): 2016-2019.
12. Cui HH, Jiang SQ. Treatment of 30 Cases of Sanyin Breast Cancer with Shugan Jianpi Jiedu Sanjie Method. Henan J Tradit Chin Med 2015; 35(9): 2196-2198.
13. Wang ZG, Lin LZ. Efficacy and safety of Shugan Jianpi Yishen Chinese medicine combined with chemotherapy in the treatment of metastatic triple-negative breast cancer patients with liver stagnation. Chin J Gen Pract 2015; 18(6): 620-624.
14. Ren XY. Clinical analysis of traditional Chinese medicine combined with chemotherapy in the treatment of metastatic triple-negative breast cancer. Pract Chin Med J 2016; (11): 1096-1097.
15. Tang R, Zhao CY. Application of Yiqi Rehabilitation in the adjuvant treatment of triple-negative breast cancer and...
its effect on immune function. Sichuan J Tradit Chin Med 2015; (12): 87-89.

16. Li Y, Huang LZ, Gong H, Zhang H, Xiao YJ, Wang YQ, Liang H. Effect of TCM Emotional Therapy on Quality of Life in Patients with Triple Negative Breast Cancer during Postoperative Recovery. J Hunan Univ Tradit Chin Med 2015; 35(10): 54-56.

17. Zheng GL, Zhang JB, Li XH, Zhao Y, Li YJ, Li JZ. Comparative study on traditional Chinese medicine in postoperative triple negative breast cancer prevention and recurrence and metastasis. Mod Oncol Med 2017; 25(2): 220-223.

18. Chen H, Yan XL, Qiu P. Effect of Integrative Chinese and Western Medicine on Survival Rate of Patients with Sanyin Breast Cancer. Anhui Med J 2014; (9): 1757-1758.

19. Huang XY. Analysis of Immunity Function Changes of Chinese Medicine for Patients with Triple-negative Breast Cancer Treated with Radiation and Chemotherapy. J Mathematical Med 2016; 29(8): 1128-1129.

20. Chen ZJ. Effect of Chinese Herbs Treatment on Survival Rate of Three-negative Breast Cancer Patients. West J Tradit Chin Med 2015; 28(9): 103-105.

21. Liang CL, Yang HJ. Research Progress on Neo-adjuvant Chemotherapy Medicine for Triple Negative Breast Cancer. J Chin Oncol 2018; 24(3): 188-194.

22. Ma J. Analysis of clinicopathological features and prognostic factors of triple negative breast cancer. For All Health 2017; 11(8): 22-23.