The use of Chinese herbal medicine to improve quality of life in women undergoing chemotherapy for ovarian cancer: a double-blind placebo-controlled randomized trial with immunological monitoring


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Background: This study aimed to evaluate traditional Chinese medicine (TCM) in improving quality of life (QOL), reducing chemotoxicity and modulating immune function in patients undergoing chemotherapy.

Patients and methods: Patients with ovarian cancer were randomized to receive either TCM or placebo in addition to standard chemotherapy. The primary outcome was global health status (GHS) score, assessed by European Organization for Research and Treatment of Cancer questionnaire, while the secondary outcomes were other QOL items, chemotoxicity according to World Health Organization criteria and alterations in immune function as measured by immune cells count and the numbers of cytokines-secreting cells.

Results: There was no significant difference in the GHS between the two groups. With adjustment for stage, chemotherapy type, disease status, age and baseline value, emotional function, cognitive function and nausea and vomiting were found to be worse or less improved in the TCM group compared with placebo group after six cycles of chemotherapy. The TCM group had less neutropenia after three cycles (0% grade 4 neutropenia versus 28.6%). There were no other significant differences in terms of chemotoxicity. Lymphocyte counts and cytokine activities decreased less in the TCM group.

Conclusions: TCM did not improve QOL but did have some effects in terms of maintaining immune function.

Key words: chemotherapy, immune function, ovarian cancer, quality of life, traditional Chinese medicine

Introduction

Ovarian cancer is the fourth commonest female cancer worldwide. The mainstay of treatment is surgery, including total hysterectomy and bilateral salpingo-oophorectomy and staging or debulking of tumors, followed by adjuvant chemotherapy. Myelosuppression, hair loss, nausea, vomiting as well as neuropathy are common in patients during chemotherapy and these side-effects, together with the emotional disturbances due to recent diagnosis of cancer and major surgery can potentially have a significant impact on the quality of life (QOL) in patients undergoing such treatment.

The use of traditional Chinese medicine (TCM) is common in cancer patients. Previous studies have shown that 28%–98% of Chinese cancer patients in Asia reported TCM use [1, 2], while 25%–47% of those living in the North America used TCM as part of their cancer care [3, 4]. TCM has been reported to alleviate chemotherapy-induced nausea and vomiting [5]. Furthermore, it was shown to possess immunopharmaceutical effects by modulating lymphocyte functions and immune effector cells [6]. Some herbal components have also demonstrated antitumor activity by improvement of immune function [7].

Although TCM is used widely, its efficacy has been studied in few properly randomized and controlled studies. We have therefore conducted a randomized, placebo-controlled trial to study whether TCM can indeed decrease the side-effects of systemic chemotherapy and improve QOL and immune status of patients undergoing standard treatment for ovarian cancers.

Methods

This was a double-blind randomized controlled trial for patients with ovarian cancers undergoing chemotherapy. The primary outcome was QOL, while the secondary outcomes were chemotherapy-related side-effects and alterations in immune function. The study was approved by the local ethical committee (IRB no. UW03-273 T/273). Informed written consent was obtained from patients who wished to participate in the study. Inclusion criteria were women with ovarian cancer who need
chemotherapy, aged over 18, Chinese ethnic origin, Cantonese or Mandarin speakers, ability to read Chinese, ability to tolerate oral intake, not given chemotherapy for at least 6 months before the planned treatment, life expectancy over 6 months. After assessment of eligibility, the patients were be randomly assigned to either a control group receiving placebo or a study group receiving TCM prescribed by an expert TCM practitioner. Randomization was done by computer-generated randomization tables by a research associate. Block randomization, in blocks of five, was stratified according to the chemotherapy regimen. The pharmacist dispensed the treatment according to the randomization results. All caregivers and patients were blinded to the results of randomization.

The study group received Chinese herbal medicine in powder form twice daily based on a formula provided by an experienced TCM practitioner (Appendix S1, available at Annals of Oncology online). The TCM formula selection was based on traditionally known medicinal properties of the individual herbs together with the experience of the practitioner. The formula was aimed for enhancing the general well being of the patient and was not intended to have any specific cytotoxic effects on ovarian cancer. All patients in the study group received exactly the same combination and amount of herbs as stated in Appendix S1 (available at Annals of Oncology online). The control group received a placebo, which mimicked the taste and appearance and was indistinguishable from the study medication. The powder was administered from the first course of chemotherapy for six courses. During the study period, all the patients were given three weekly cycles of platinum-based chemotherapy for ovarian cancer for a total of six cycles. The patients received either carboplatin (AUC = 6) alone or in combination with paclitaxel (Taxol) (175mg/m²) according to their disease status. All patients received standard prechemotherapy antiemetics. The patients were monitored regularly by gynecological oncologists for side-effects and response to chemotherapy and also by the TCM practitioners. The latter had received recognized training in China and were licensed to practice in Hong Kong and China. During review, as per TCM practice, adjuvant herbs were given according to the condition of the patients.

**measurement of outcomes**

QOL was measured by the validated Chinese version of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 [8]. The questionnaire was completed by the patients at baseline, after the third cycle of chemotherapy and 6 weeks after the sixth cycle. The primary end point was the global health status (GHS) score (GHS) with all the function and symptom scores as secondary end points.

The side-effects of treatment were monitored using the World Health Organization (WHO) criteria. Complete blood pictures, liver and renal function tests were checked 2 weeks after each chemotherapy cycle to detect any hematological, hepatic or renal toxicity.

The extent of immunomodulation was evaluated by in vitro cytokine and natural killer (NK) cell activities and phenotypic analysis of peripheral blood mononuclear cells by flow cytometry. The tests were carried out on the day of the first course of chemotherapy before the administration of the chemotherapeutic agent and TCM and were repeated before the fourth course and at 4 weeks after the completion of sixth course of chemotherapy. Numbers of cytokine-secreting cells in unstimulated cultures or cultures stimulated with T-cell activators phytohaemagglutinin (PHA), Concanavalin A (Con A) or monocyte activator *Staphylococcus aureus* Cowan I (SAC) were determined using enzyme-linked immunosorbent spot (ELISPOT) assays [9]. Details of our adaptation of this method and its specificity, reproducibility and clinical utility have been previously described [10, 11]. NK activity was measured by MTT assay with K562 as the target cells and lymphocyte subsets by flow cytometry of whole blood after duel color staining using standard methods.

**sample size calculation and statistical analysis**

It was reported that women with advanced ovarian cancer receiving chemotherapy, the mean GHS score at the day of cycle 4 was 67 ± 21 [standard deviation (SD)] [12]. Assuming that about half of the SD, that is, a 11-point difference would be clinically significant [13], a sample size of 57 in each group would give a power of 80% to detect the difference with a maximal false-positive rate of 5%. The total sample size would be 114.

Student’s t-test or Chi-square test was used to compare the two groups for baseline characteristics. For QOL assessment, sample mean scores for the different items were calculated for each group at baseline and after the third and sixth cycle of chemotherapy. Between-group and within-group differences of the scores were explored with Student’s t-test and paired Student’s t-test, respectively. Generalized linear model was used to compare each QOL item assessed in the questionnaire between treatment groups after

Table 1. Background characteristics

<table>
<thead>
<tr>
<th></th>
<th>Study (TCM), n = 31</th>
<th>Control, n = 28</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age (mean)</td>
<td>52.9</td>
<td>51.5</td>
<td>0.587*</td>
</tr>
<tr>
<td>Stage</td>
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<td>Stage 1</td>
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<td>0.316*</td>
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<tr>
<td>Stage 2</td>
<td>2</td>
<td>4</td>
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<tr>
<td>Stage 3</td>
<td>11</td>
<td>8</td>
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<tr>
<td>Stage 4</td>
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</tr>
<tr>
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<td>1</td>
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<tr>
<td>Chemotherapy intent</td>
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</tr>
<tr>
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<td>26</td>
<td>21</td>
<td>0.662*</td>
</tr>
<tr>
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<td>5</td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
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<td>2</td>
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<tr>
<td>Chemotherapy agent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carboplatin + taxol</td>
<td>29</td>
<td>25</td>
<td>0.557*</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>2</td>
<td>3</td>
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</tr>
</tbody>
</table>

* t-test.
* Chi-square test.

TCM, traditional Chinese medicine.
three cycles or six cycles, adjusting for background characteristics and the 
baseline value of the compared QOL item. For side-effects, chi-square test was 
used to explore any significant difference in severity (by grades) between the 
two groups. For immune function, including lymphocyte and cytokines 
activities, median levels were calculated for each group and between- and 
within-group differences were assessed by Mann–Whitney test and Wilcoxon 
signed-rank test, respectively. For all secondary end points, the 
$p$ values were 
not adjusted for multiple testing due to the exploratory nature. All statistical 
analyses were carried out using SPSS 16.0 (SPSS Inc, Chicago, IL).

**Interim analysis**

The recruitment rate was slower than expected. A unplanned interim 
analysis was conducted after 52% of the target number completed the 
study. We found that the mean global health score obtained in the TCM 
and the placebo groups were 60.48 and 61.61, respectively, and the pooled 
estimate of SD was 17.55. If the current trend continued to the end of the 
study, the conditional power [14], that is, the chance of obtaining a significant result and declaring the TCM group had higher GHS score than the placebo group was 0.05%. Even if the TCM group was truly better and we continued to recruit until 114 patients completed the study, the conditional power was just 11%. We felt that it was unlikely to have 
a different conclusion even when we reached the target sample size and the study was therefore terminated prematurely.

**Results**

Eighty-one patients were recruited into the study between May 
2004 and October 2006. Forty were randomized to the study 
group and 41 to the control group. Fifty-nine (72.8%) patients 
completed the study, 31 in the study group and 28 in the control 
group (Figure 1). There was no significant difference between the 
study and control group in terms of age, stage of the disease, 
disease status or chemotherapy agents used (Table 1).

**QOL – GHS and functional scales**

The scores for the GHS, physical, role, emotional, cognitive and 
social functioning are shown in Figure 2. There were no 
significant differences between the two groups for GHS score at 
baseline [57.26 ± 3.68 (mean ± standard error) for study 
group versus 55.06 ± 4.01 for control group], after three cycles 
(60.18 ± 3.35 versus 61.61 ± 3.07) and after six cycles (66.40 ± 3.99 versus 65.18 ± 2.75) of chemotherapy. For within-group
two groups were statistically significant (in the control group (7.14

Figure 3. Quality of life (QOL) scores for symptom scales items. **P value <0.05 (using paired T test), ##P value <0.05 (using T test).
comparisons, there were also no significant changes in the GHS after three cycles in each group and after six cycles, only the control group showed significant improvement (mean change of score from baseline: 10.12 ± 4.68, \( P = 0.04 \)).

For other QOL scores in the function scales after cycle 3, there were no significant differences between the two groups. For within-group comparisons, both groups had significantly improved physical (mean change of score: 11.61 ± 4.77, \( P = 0.021 \) and 11.67 ± 4.52, \( P = 0.016 \) for study and control group, respectively) and role function compared with baseline (mean change of score: 24.73 ± 7.84, \( P = 0.004 \) and 16.67 ± 7.42, \( P = 0.033 \), respectively). The control group had better emotional function (mean change of score: 14.88 ± 4.78, \( P = 0.004 \)), but only marginal improvement was seen in the study group (mean change of score: 8.60 ± 4.90, \( P = 0.089 \)). Scores for cognitive function tended to be worse in the study group (−9.14 ± 5.12) compared with baseline but better in the control group (7.14 ± 4.81) and the change between the two groups were statistically significant (\( P = 0.025 \)). There were no significant changes in social function in either group.

After six cycles, there were again no significant differences between the two groups in the function scale scores but for within-group comparisons, both groups had significantly improved physical (mean change of score: 15.49 ± 5.20, \( P = 0.007 \) and 15.00 ± 4.70, \( P = 0.003 \) for study and control group) and role functions (mean change of score: 29.03 ± 9.26, \( P = 0.004 \) and 27.98 ± 7.24, \( P < 0.001 \) compared with baseline. Social and emotional functions were significantly improved in the control group (mean change of score: 16.07 ± 7.13, \( P = 0.025 \) and 17.56 ± 5.23, \( P = 0.002 \), respectively) but not in the study group (6.45 ± 8.33 and 2.96 ± 5.10, respectively). There were no significant changes in the cognitive function in either group. In comparison, the control group improved more in emotional function and in social function after cycle 6, but the change between the two groups was only significantly different for emotional function (\( P = 0.049 \)). The study group did not show any superiority in any of the functional scale aspects.

Multiple regression analysis confirmed that adjusting for age, stage, chemotherapy intent, chemotherapy agent and baseline value and GHS score were not statistically different between the two groups after three or six cycles. With adjustment, cognitive function score was worse in study group after three cycles (adjusted difference: 13.9, 95% confidence interval (CI) 2.8–25.1) and after six cycles (adjusted difference: 12.4, 95% CI 0.3–24.4); and emotional function score improved less in study group after six cycles (adjusted difference: 14.5, 95% CI 3.1–26.0).

QOL – symptoms scale
The scores for appetite loss, nausea and vomiting, constipation, diarrhea, dyspnoea, fatigue, insomnia and pain are shown in Figure 3. There were no significant differences between the two groups for symptom scores, except for insomnia at baseline (33.33 ± 5.35 and 52.38 ± 6.73 for TCM and placebo groups, respectively, \( P = 0.048 \)). After three cycles, both fatigue (mean change of score: −12.19 ± 5.77, \( P = 0.043 \) and −21.83 ± 5.25, \( P < 0.001 \) for study and control group, respectively) and pain (mean change of score: −20.43 ± 6.94, \( P = 0.006 \) and −13.10 ± 4.88, \( P < 0.012 \), respectively) were significantly better for both groups. Dyspnoea was significantly improved in the control group only (mean change of score: −17.86 ± 6.06, \( P = 0.007 \)) and the score was significantly different between the two groups (\( P = 0.035 \)). Insomnia was worse in the study group (mean change of score: 22.58 ± 8.09, \( P = 0.009 \)), although the score after cycle 3 between the two groups was not significantly different. There was a trend for less diarrhea in the study group (−9.68 ± 4.94) compared with baseline but more diarrhea in the control group (8.33 ± 5.59). These within-group changes were not significant but the actual score for diarrhea turned out to be significantly higher in the control group (5.38 versus 16.67 for study and control group, respectively, \( P = 0.046 \)) after cycle 3. In comparing, these changes in symptoms between the two groups after three cycles, dyspnoea was significantly better in the control group (\( P = 0.014 \)), insomnia was significantly worse and diarrhea was significantly better in the study group (\( P = 0.17 \) and \( P = 0.019 \), respectively).

After six cycles, there were no significant differences in all the scores between the two groups. For within-group comparisons, fatigue (mean change of score: −17.20 ± 6.864, \( P = 0.017 \)
and $-24.60 \pm 5.99$, $P < 0.001$ for study and control group, respectively) and pain (mean change of score: $-23.12 \pm 6.15$, $P = 0.001$ and $-23.21 \pm 6.41$, $P = 0.001$, respectively) remained to be significantly better for both groups. There was also significant improvement in dyspnoea (mean change of score: $-14.29 \pm 7.23$, $P = 0.031$), appetite ($-28.57 \pm 7.57$, $P = 0.001$) and constipation ($-17.56 \pm 7.14$, $P = 0.022$) in the control group, but not in the study group compared with baseline and there was no significant difference in the insomnia or diarrhea score in either group. Also, none of these changes were significantly different between groups.

Multiple regression analysis showed that adjusting for age, stage, chemotherapy intent chemotherapy agent and baseline value, dyspnoea score improved more in the control group (adjusted difference: 14.6, 95% CI 2.0–27.2) and diarrhea score improved more in the study group (adjusted difference: 10.8, 95% CI 0.6–21.0) after three cycles; while nausea and vomiting score were worse in study group after six cycles (adjusted difference: 12.1, 95% CI 0.6–23.5). The exact QOL scores and estimates of regression coefficients were shown in Appendices S2 and S3 (available at Annals of Oncology online).

### Chemotherapy-induced toxicity

Chemotherapy-induced toxicity as assessed by the WHO criteria is summarized in Table 2. The commonest side-effect was alopecia, with 44% and 67% of patients developing grade 3 alopecia at the end of the third cycle and sixth cycle, respectively. After both the third cycle and sixth cycle of chemotherapy, there were no significant differences between the study and control groups in the severity of the side-effects from chemotherapy, including nausea and vomiting, diarrhea, stomatitis, alopecia and skin problems but TCM group had significantly worse neuropathy after cycle 6. Assessment for severity of myelosuppresion was shown in Table 3. After cycle 3, the control group had significantly worse neutropenia compared with the study group, with eight (28.6%) patients having grade 4 neutropenia compared with none in the study group. However, the difference in neutropenia was not significant after cycle 6. There were no significant differences in terms of hemoglobin, total white cell count or platelets between the two groups after either cycle 3 or cycle 6.

### immune function

Total white blood cells dropped significantly in both groups at both cycles 3 and 6 compared with baseline ($P < 0.001$). Total lymphocyte count in the control group dropped significantly at cycle 3 and cycle 6 when compared with baseline ($P = 0.005$ and $P = 0.002$, respectively) but the levels were maintained in the study group. The drop was mainly due to a decrease in B lymphocytes rather than T lymphocytes. There was a significant reduction in the control group after cycle 3. However, by cycle 6, both groups
showed a significant decrease. There was no significant change in T lymphocyte counts, including CD4+ and CD8+ T cells, in either group after three or six cycles. In the control group, there was asignificant drop in NK cells after both cycles 3 and 6, but there was no significant change in the NK activity (Figure 4).

After three cycles of chemotherapy, most cytokines measured, including interleukin (IL)2 con A, IL4 PHA, IL6 PHA/SAC, TNFa PHA/SAC and IFNg con A, showed a significant decrease in the control group but not in the study group compared with the baseline (Figure 5). For IL10, there was a significant decrease for both groups. After six cycles, IL4 PHA, IL6 PHA and TNFa PHA/SAC were significantly lower than the baseline in the control group, but the difference in the study group was not significant. IL10 was significantly lower in both groups after both three and six cycles. There was no significant change in IL2, IL12 and IFNg after six cycles in either group.

discussion

Prescription of traditional Chinese herbal medicine typically consists of a formula with a number of different herbal components, with each component having its own characteristic functions in order to produce an overall synergistic effect. The formula used for the study group consisted of a combination of a number of herbs. Each ingredient included was well established in TCM use, but the exact amount and combination were determined by the practitioner. The formula was aimed at reducing the chemotherapy-induced side-effects but some of the herbs included were also shown to have anti-oxidant and cytotoxic activities [15–17] and they might also enhance cellular immunity [18–20]. It was hoped that this formula would improve the overall QOL for women undergoing chemotherapy. However, our study demonstrated no overall improvement in QOL. On the contrary, improvement in emotional function was significantly less in the study group. In general, any improvements in patients taking TCM might be due to a ‘placebo’ effect, as most subjects believe that TCM would be beneficial. In this study, since the control group also had a placebo medication, this effect was abolished. The formula used did not specifically include ingredients targeting at emotional function. It was initially anticipated that by improving their overall symptoms, emotional status would improve. However, our study did not show any significant improvement in symptoms in the study group. In the absence of improvement in symptoms, it was unlikely that the patients would have any significant improvement in their emotional status and overall QOL. Interestingly, physical function scores improved significantly from baseline during chemotherapy for both groups. Since most patients underwent major cancer surgery just before chemotherapy, the improvement in physical function might be a reflection of the gradual recovery from surgery.

Similar to another randomized trial on Chinese herbal medicine for reduction of chemotherapy-related toxicity [21], we did not find any significant difference in the severity of anaemia or thrombocytopenia between the study and control groups. However, in contrast to the results from that trial, we found that neutropenia was less in the study group. Preparations containing Codonopsis (Dang shen) and Fu Ling, ingredients in our study group, were reported to augment the secretion of granulocyte–macrophage colony-stimulating factor [22]. Reduction of neutropenia is clinically important in patients undergoing chemotherapy as this would prevent delay in treatment due to significant neutropenia as well as prevent serious complications such as neutropenic fever.
TCM is believed to alter immune function. It has been hypothesized that herbal medicine would modulate the autonomic nervous system [23], which has been linked to the control of granulocyte, lymphocyte and NK cell counts [24–26]. In agreement with this, we found that the study medication helped to maintain overall lymphocyte counts, with more effect on B lymphocytes than T lymphocytes. Theoretically, with maintenance of B-cell counts, there would be better humoral immunity and more protection against bacterial infection, but the actual clinical impact was not evaluated in this study.

Apart from alterations in lymphocyte counts, our study also found that TCM appeared to maintain cytokine activity. Cytokines have been reported to be altered by botanical therapies, e.g. *Poria cocos*, one of the ingredients included in the study group, was known to increase IL6 and TNF secretion [21]. IL6 levels had been associated with cognitive impairment [27] and depression in cancer patients [28, 29]. We found that the IL6 levels remained high in the study group but not in the control group. This might explain the worse scores in cognitive function and less improvement in emotional function in the study group. Overall, our findings suggested that TCM might be able to maintain immune activities, but whether such immune profiles would improve the overall well being or long-term prognosis needs further investigations.

We felt that in order to evaluate the true relative values for different treatment modalities, it was important to use the same standardized tools. In this study, we have used well-established standardized international assessment tools such as EORTC or WHO criteria to measure the effect of TCM, which traditionally had been assessed by completely different criteria. For measuring cytokines’ production, ELISPOT assays were used. This method has advantages over methods such as flow cytometry or reverse transcriptase PCR because it measures the actual secreted cytokines instead of intracytoplasmic proteins or message. It also avoids the problem of cytokine neutralization by concomitantly secreted antagonists or soluble receptors, which affects measurement of cytokines in culture supernatants.

Although we only tested a single TCM formula, provided by the well-qualified practitioner, the standard of care provided was typical of, if not better than, that provided by TCM practitioners in Hong Kong in general. Unfortunately, we failed to collect background data on patients’ social situation, such as occupation, marital status, family income, etc, which might have impact on QOL. Another drawback was the addition of herbs to
the existing formula/placebo during the review by the TCM practitioner, who felt that this was an inherent component in TCM patient care. Ideally, these adjuvant herbs should also be controlled for but this was not included in the trial design, as it was not anticipated initially that adjuvant herbs would be necessary. This resulted in the both the study and placebo group receiving herbs outside the study formula. However, as this was a randomized trial, it was hoped that the difference between the two groups would not be significant and the overall results would not be affected. The study was terminated early as we failed to recruit adequate number of patients to meet the initial calculated sample size, mainly due to patient refusal to join the study. Patients who were interested in TCM would prefer to take TCM without being involved in a randomized trial.

conclusions
Overall, our findings suggested only a limited role for TCM to improve QOL in women undergoing chemotherapy but it might have some beneficial effect by reducing severe neutropenia. Our findings agreed with previous literature that immune function was altered by TCM. However, from our study, it was unclear how this would translate into clinical benefits. Since TCM is a package of care including combination of different herbs, together with adjustment of treatment according to the continuous review of the patient’s condition, instead of using a single fixed drug as in most western conventional treatment, it is important to test the whole package of care in the clinical setting rather than to evaluate the possible biochemical effects of the constituents of a single herb, as done in most other studies on TCM in western literature. Although there is a large number of published reports on TCM use in cancer patients, results from trials done with rigorous scientific methods, i.e. randomized controlled trials with standardized measurable end points, are still scanty. Both our study and the only other randomized trial of herbal medicine failed to recruit sufficient study numbers and had to be terminated early [30]; evidently, conducting such trials are practically very difficult. Nonetheless, in order to fully evaluate the merits of TCM in cancer patients, continued effort in conducting scientifically sound studies are warranted.
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