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ORIGINAL ARTICLE

Evaluation of chemotherapy-induced toxicity and health-related quality of life amongst early-stage breast cancer patients receiving Chinese herbal medicine in Malaysia

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Abstract

Purpose This observational study aimed to compare the outcome and health-related quality of life (HRQOL) amongst breast cancer patients using Chinese herbal medicine (CHM) and those not using CHM during chemotherapy.

Methods A prospective, non-randomised longitudinal study was conducted in two government integrated hospitals over an 8-month period. Early-stage breast cancer patients who were (1) either already using complementary and alternative medicine (CAM) or not and (2) who were on a regime of 5-fluorouracil, epirubicin, and cyclophosphamide were included in the study. Patients who agreed to receive CHM were assigned to receive individualised CHM prescriptions deemed suitable for the individual at a particular time. Those who were not willing to take Chinese herbal medicines (CHM) were assigned to the non-CHM control group. Blood profile and chemotherapy-induced AE were recorded whilst HRQOL assessment was done using the EORTC QLQ-C30 questionnaire on first, third, and sixth cycles.

Results Forty-seven patients [32 female vs. 1 male, $p = 0.31$; mean year of age: 52.2($SD = 7.6$), $p = 0.28$)}] were recruited during the study period. Demographics of both groups were comparable. Fifty percent of respondents reported using some kind of CAM before chemotherapy. Diet supplements (40.6%) were the most common CAM used by the respondents. The study showed that patients using CHM had significantly less fatigue ($p = 0.012$), nausea ($p = 0.04$), and anorexia ($p = 0.005$) during chemotherapy. There were no significant differences in patients' HRQOL ($p = 0.79$). There were no AEs reported during the study.

Conclusion The use of CHM as an adjunct treatment with conventional chemotherapy have been shown to reduce fatigue, nausea, and anorexia in breast cancer patients but did not reduce chemotherapy-associated hematologic toxicity. The sample size of this study was not powered to assess the significance of HRQOL between two groups of patients.

Keywords Chinese herbal medicine · Integrated medicine · Health-related quality of life · Chemotherapy-induced adverse events · Breast cancer

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Introduction

The use of complementary and alternative medicine (CAM) also known as traditional and complementary medicine (T&CM) in Malaysia is increasing amongst healthy individuals as well as patients with chronic diseases [16]. Cancer patients believe that CAMs have the ability to reduce adverse effects of conventional treatments, can increase the efficacy of conventional treatments, and may reduce the risk of cancer relapse [36]. However, these claims require evaluation regarding efficacy and safety in the process of integrating CAMs with conventional medicines in cancer care.

A national survey on CAM in 2004 showed that 69.4% (67.6–71.2%) of Malaysians have tried using T&CM during their lifetime, whilst 55.6% (53.8–57.4%) of Malaysians have used CAM products during over the past 12 months before the survey [39]. Females are the most common CAM users in Malaysia [2, 10, 12, 29, 36].

CHM, a herbal treatment system using traditional Chinese medicine (TCM) approach, which is characterised by holism and treatment based on pattern identification/syndrome differentiation. It is one of the major forms of CAM, is becoming increasingly popular in many medical contexts worldwide. For instance, a study showed that 56% of breast cancer patients reported CAM usage whilst 46.5–48.5% reported TCM use and more than half of patients (53.6%) were taking CHM in Singapore [38]. Systematic reviews showed that CHM and acupuncture are effective in the treatment of atopic eczema, chemotherapy-induced nausea, and gynaecology conditions such as infertility [6, 8, 35, 41]. In fact, CHM has been used to reduce chemotherapy-induced toxicities and to increase their health-related quality of life (HRQOL) [7, 23]. Yet, evidence of the efficacy of TCM in reducing chemotherapy-induced toxicities is still lacking.

This study is the first of its kind being conducted in Malaysian government integrated hospitals on the use of CHM concomitant with chemotherapy. Therefore, the results of this study will pave the way to future research studies in Malaysia.

This study aims to determine the chemotherapy-induced toxicities in hematologic and non-hematologic profiles of breast cancer patients (which is the most common cancer amongst women [19]) and cancer-related symptoms in both the CHM group and non-CHM group. The secondary objective of this study is to assess the HRQOL of breast cancer patients with CHM and without CHM, to analyse the prevalence of CAM in breast cancer patients, determine patients' demographics, and identify adverse effects in chemotherapy patients receiving CHM concomitantly.

Materials and methods

Procedure

This study was a prospective longitudinal prospective study conducted in two day-care centres in Penang General Hospital (PGH) and Kepala Batas Hospital (KBH). The catchment area for these two facilities was Penang state. Convenience sampling was used to select eligible patients who were willing to participate in this study from December 2011 to August 2012. The study population comprised primary breast cancer patients without metastasis, who were 25–70 years of age receiving 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy treatment. Patients with chronic diseases, abnormal liver, and renal function were excluded in this study. Eligible subjects, who were recommended by oncologists, were assigned to two groups according to their choice. Those unwilling to receive CHM were assigned to the non-CHM control group. The non-CHM group of breast cancer patients was treated with standard FEC treatment only. A written consent letter was obtained from all patients participating in this research study.

CHM group

Subjects, who agreed to receive CHM, were assigned to Traditional & Complementary Medicine (T&CM) Unit, KBH to start CHM regime before their first cycle of chemotherapy. Subjects visited T&CM unit every 14 days. The T&CM unit herbalist evaluated the patients according to CHM approach and prescribed a combination of single-itemised herbs from the herbal pharmacy. However, the duration of CHM supply may vary according to the patient's condition. Patients with stable conditions might receive a 28-day herbal supply upon practitioner's judgement. Patients need to mix and dissolve all the single herbs, which are prescribed by herbalist with hot water and drink it twice a day before meal.

Eighty-one types of single herbs were packed in sachet form (Appendix). Each sachet contained 2 g of water-soluble herbal granules that were manufactured at a Good Manufacture Practice standard facility (Kaiser Pharmaceutical Ltd., Taiwan). Each herb was boiled in water and the liquid extract was dehydrated by nebulization dehydration method. Quantified in dry weight were pack into sachet and was labelled with a serial number.

Sample size and sampling method

The sample size of this study was based on the validity of assumptions and clinical experience of the past [28, 40]. The sample consisted of 36 patients (18 patients in each arm), enabling an 80% power of detecting a 45% difference between the CHM group (60% of reduction of chemotherapy

toxicity) and non-CHM group (15% of reduction of chemotherapy toxicity), which is a clinically significant difference after accounting for a 30% dropout rate, with a 95% confidence level [26].

Measurement tools

A self-reported questionnaire was constructed to assess the patients' demographic, disease information, and CAM use.

Patients' chemotherapy-induced toxicity was assessed using a common terminology criterion of adverse events (CTCAE) version 4 which is constructed by the National Cancer Institute in the USA [32]. It is a terminology which has been widely used for adverse events (AEs) and adverse drug effects (ADE) reporting in cancer treatment. The importance of CTCAE lies in its grading system of AEs in oncology therapeutic trials and the degrees of AEs in affecting patients' activities of daily living (ADL) in a standard and uniform way.

HRQOL was assessed by using a self-administered questionnaire, the EORTC QLQ-C30. The EORTC QLQ-C30 has demonstrated validity and reliability in breast cancer patients. All versions of QLQ-C30 incorporated five functional scales (physical, cognitive, role, emotional, and social). Also included were a three-symptom scale (fatigue, pain and nausea, and vomiting), a global health status or QOL scale, and a number of single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) and perceived financial impact of the disease [13]. Development and validation of the QLQ-C30 have been published. A Scoring Manual is available for QLQ-C30 [1]. The Reference Values Manual provides values based upon international data sets from many countries [37].

Medical follow-up record tracing form and the patient's diary act as a self-filled out document to check on patients' compliance to their treatment in the T&CM unit.

Adverse effects of CHM were recorded if the patients suspected having any unwanted adverse effects of CHM. They were transferred back to the CHM practitioner and the oncology doctor for further investigation. Close monitoring and causality assessment such as the physical evaluation by the physician, related laboratory tests were given to the subjects, and Naranjo's algorithm was used to identify the adverse effects, whether they were related to CHM, chemotherapy, or due to the disease itself [30].

Data collection procedure and follow-up procedure

The self-administered EORTC QLQ-C30 was distributed to research subjects before they started their first, third, and sixth cycles of chemotherapy. Assessment of the chemotherapy-induced toxicity was done on the third day after the chemotherapy through phone interviews on the first, third, and sixth cycles of chemotherapy. Full blood count, liver function, and renal function were taken before every cycle of chemotherapy. Each patient was responsible for completing a patient diary entry with regard to each day's consumption. A structured interview using Morisky Medication-taking adherence scale was performed during the first, third, and sixth cycles of chemotherapy. A medical follow-up record tracing form was used for tracking patients' adherence to CHM therapy. More than one method of collecting data was used as it has the potential to increase the response rate, participant representativeness, and enhance the precision of effect estimates [20].

Statistical analysis

The outcome of chemotherapy-induced AEs, adherence, and HRQOL were analysed using Statistical Package for the Social Sciences (SPSS) version 20. Chemotherapy-induced toxicities under CTCAE v4.0 and patients' demographics were categorised into groups, whilst blood profile readings were recorded as continuous variables.

The normality of the demographic data was tested by Shapiro-Wilk test, and the result showed the data were normally distributed ($p > 0.05$). Therefore, a parametric test was used for the evaluation. All p values were two-tailed, and the α level of significance was set at 0.05. Significance difference between each variable was analysed using chi-squared test or Fisher's exact test.

Descriptive results were presented as frequencies and percentages for categorical variables, whilst mean (± SD) for continuous variables was analysed using independent t test.

Ethical approval

The study proposal was registered with the Malaysian National Medical Research Registry (NMRR-11-327-9060) and was approved by the Malaysian Medical Research Ethics Committee.

Results

Baseline demographic

Baseline demographics such as age, race, and socio-economic factors of the two groups were comparable (Table 1). The median age for those in the CHM group was 53 years old whilst the non-CHM group was 50 years of age. Half of the subjects were using at least one form of CAM before or during chemotherapy (50.0%, $n = 16$). Supplements (40.6%, $n = 13$) and diet modifications (25.0%, $n = 8$) were the most commonly used CAM therapies amongst the subjects. Disease stage and biomarkers of the two groups were also comparable (Table 2).

Table 1 Patients' demographic profile of CHM and non-CHM groups

	CHM, *n* (%)	Non-CHM, *n* (%)	Total, *n* (%)	*p* value
Number of patients	16	16	32	
Age (years)				
Mean (SD)	53.9 (7.4)	51 (7.7)	52.2 (7.6)	0.28
Median	53	50	52	
Range	44–68	40–66	40–68	
Gender (male vs. female)	0:16 (100)	1:15 (6.2: 93.8)	32 (100)	0.31
Race				
Malay	5 (31.2)	8 (50.0)	13 (40.6)	0.36
Chinese	10 (62.5)	6 (37.5)	16 (50.0)	
Indian	1 (6.2)	2 (12.5)	3 (9.4)	
Religion				
Muslim	4 (25.0)	8 (50.0)	12 (37.5)	0.18
Christian	2 (12.5)	0 (0.0)	2 (6.2)	
Buddhist	9 (56.3)	6 (37.5)	15 (46.9)	
Hindu	0 (0.0)	2 (12.5)	2 (6.2)	
Others	1 (6.3)	0 (0.0)	1 (3.1)	
Marital status				
Single	3 (18.8)	0 (0)	3 (9.4)	0.13
Married	13 (81.2)	15 (93.8)	28 (87.5)	
Widow	0 (0.0)	1 (6.2)	1 (3.1)	
Education level				
Illiterate	2 (12.5)	0 (0)	2 (6.2)	0.15
Primary school	1 (6.2)	5 (31.2)	6 (18.8)	
Secondary school	11 (68.8)	8 (50.0)	19 (59.4)	
University/polytechnic/college of education	2 (12.5)	3 (18.8)	5 (15.6)	
Profession/occupation				
Housewife	4 (25.0)	6 (37.5)	10 (31.2)	0.75
Teacher	5 (31.2)	4 (25.0)	9 (28.1)	
Others	7 (43.8)	6 (37.5)	13 (40.6)	
Level of income				
< RM1500/ month	7 (43.8)	8 (50.0)	15 (46.9)	0.38
RM1501–RM3000/ month	6 (37.5)	6 (37.5)	12 (37.5)	
RM3001–RM5000/month	3 (18.8)	2 (12.5)	5 (15.6)	
Complementary and alternative medicine				
No	8 (50.0)	8 (50.0)	16 (50.0)	1.00
Yes	8 (50.0)	8 (50.0)	16 (50.0)	
Type of complementary and alternative medicine				
N/A	4 (25.0)	5 (31.2)	9 (28.1)	0.61
Diet modification	5 (31.2)	3 (18.8)	8 (25.0)	
Supplement	6 (37.5)	7 (43.8)	13 (40.6)	
TCM	1 (6.2)	0 (0.0)	1 (3.1)	
Herbal medicine	0 (0.0)	1 (6.2)	1 (3.1)	
Disease been diagnosed (month)				
1	2 (12.5)	3 (18.8)	5 (15.6)	0.78
2	5 (31.2)	3 (18.8)	8 (25.0)	
3	4 (25.0)	4 (25.0)	8 (25.0)	
4	4 (25.0)	5 (31.3)	9 (28.1)	
5	0 (0.0)	0 (0.0)	0 (0.0)	
6	1 (6.3)	0 (0.0)	1 (3.1)	
Missing data	0 (0.0)	1 (6.3)	1 (3.1)	
Treatment month				

Table 1 (continued)

	CHM, *n* (%)	Non-CHM, *n* (%)	Total, *n* (%)	*p* value
0	2 (12.5)	0 (0.0)	2 (6.2)	0.5
1	3 (18.8)	5 (31.2)	8 (25.0)	
2	5 (31.2)	7 (43.8)	12 (37.5)	
3	4 (25.0)	2 (12.5)	6 (18.8)	
4	2 (12.5)	2 (12.5)	4 (12.5)	
Type of chemotherapy				
Adjuvant	13 (81.2)	15 (93.8)	28 (87.5)	0.6
Neoadjuvant	3 (18.8)	1 (6.2)	4 (12.5)	

Note. CHM Chinese herbal medicine, N/A not applicable

CTCAE

For the blood and lymphatic disorder, the CHM group did not show any significant differences over the non-CHM group in anaemia and febrile neutropenia over 6 cycles.

CHM group showed benefit over the non-CHM group for severe nausea in the sixth cycle of chemotherapy ($p = 0.04$) (Fig. 1). Sixty-nine percent ($n = 11$) of patients in the non-CHM group experienced severe vomiting vs. 25.0% ($n = 4$) in the CHM group. However, there were no significant advantages in vomiting, constipation, and diarrhoea in either group.

The CHM group also had better results over the non-CHM group in the sixth cycle with regard to anorexia in metabolism and nutritional disorders (Fig. 2). However, there were no significant differences in hypernatremia, hyponatremia, hyperkalaemia, and hypokalaemia.

With regard to fatigue, the CHM group showed an overall benefit in the sixth cycle of fatigue over the non-CHM group ($p = 0.012$) (Fig. 3). Twenty-five percent ($n = 4$) of those in the CHM group did not feel fatigue compared to 12.5% ($n = 2$) of the non-CHM group.

Blood profile

For blood profile, there were no significant differences between the non-CHM group and CHM group after the sixth cycle of chemotherapy (Table 3).

HRQOL-EORTC QLQ-C30 scoring analysis

The non-CHM group experienced better cognitive function (88.24 vs. 76.04; $p = 0.004$) and scored lower in sleeping disturbance in the baseline scoring (9.8 vs. 27.08; $p = 0.04$) but not after the third cycle. CHM group had lower scores in every functional item when compared with the non-CHM group, except for the physical function ($p = 0.64$) and global quality of life ($p = 0.79$). The cognitive function was the only functional item showing a significant difference in the sixth cycle of chemotherapy between CHM group vs. non-CHM group (69.79 vs. 85.42, $p = 0.004$).

There were no significant differences in HRQOL between the two groups in terms of changes between the raw scores of EORTC QLQ-C30 at baseline and after the sixth cycle. Neither were there any other clinically significant differences seen at the end of the study.

Toxicity and tolerability: adverse effects of CHM

No adverse reactions due to CHM were reported in this study.

Discussion

Prevalence of CAM usage amongst chemotherapy patients

A higher percentage of patients in this study (50%) were taking some kind of CAM product before or during their chemotherapy, compared with reported rates in Europe (14.8 to 73.1%) [29], as well as other regions [9, 31, 33]. The high usage of CAM may be due to the fact that Malaysia has a population comprised of diverse cultures and ethnicities. The people still follow generations of traditional healing practices, which are easily accessible and more affordable than Western treatments [26]. It has been confirmed by one study in Malaysia how the strong belief in traditional medicine is one of the main reasons which contributes to CAM use [17]. The higher percentage of Chinese in the CHM group may be attributed to their higher level of familiarity with CHM, which is their traditional ethnic medicine [26, 27].

Common terminology criteria for adverse events

The finding that the CHM group had better fatigue, anorexia, and nausea profile in the sixth cycle of chemotherapy when compared with the non-CHM group was consistent with that of other studies [5, 15, 21].

Table 2 Clinical presentation of the respondents for CHM and non-CHM group

	CHM, *n* (%)	Non-CHM, *n* (%)	Total, *n* (%)	*p* value
ECOG performance status				
0	14 (87.5)	13 (81.2)	27 (84.4)	1.0
1	2 (12.5)	3 (18.8)	5 (5.6)	
Side of breast cancer				
Right	10 (62.5)	6 (37.5)	16 (50.0)	0.3
Left	6 (37.5)	9 (56.2)	15 (46.9)	
Both	0 (0)	1 (6.2)	1 (3.1)	
Primary tumour				
T1	1 (6.2)	3 (18.8)	4 (12.5)	0.5
T2	12 (75.0)	9 (56.2)	21 (65.6)	
T3	3 (18.8)	3 (18.8)	6 (18.8)	
T4	0 (0.0)	1 (6.2)	1 (3.1)	
Lymph node involvement				
Nx	3 (18.8)	0 (0.0)	3 (9.4)	0.3
N0	4 (25.0)	5 (31.2)	9 (28.1)	
N1	4 (25.0)	8 (50.0)	12 (37.5)	
N2	2 (12.5)	1 (6.2)	3 (9.4)	
N3	3 (18.8)	2 (12.5)	5 (15.6)	
Metastasis				
Mx	16 (100.0)	14 (87.5)	30 (93.8)	0.5
M0	0 (0.0)	2 (12.5)	2 (6.2)	
Oestrogen receptor				
Positive	15 (93.8)	11 (68.8)	26 (81.3)	0.1
Negative	0 (0.0)	4 (25.0)	4 (25.0)	
Missing data	1 (6.3)	1 (6.3)	2(12.5)	
Progesterone receptor				
Positive	14 (87.5)	11 (68.8)	25 (78.1)	0.3
Negative	1 (6.3)	4 (25.0)	5 (15.6)	
Missing data	1 (6.3)	1 (6.3)	2 (6.25)	
Cell type				
IDC	13 (81.3)	13 (81.3)	26 (81.3)	1.0
LCIS	2 (12.5)	2 (12.5)	4 (12.5)	
Missing data	1 (6.3)	1 (6.3)	2 (6.3)	
Grade				
G1	0 (0.0)	2 (12.5)	2 (6.3)	0.4
G2	7 (43.8)	6 (37.5)	13 (40.6)	
G3	5 (31.3)	5 (31.3)	10 (31.3)	
Missing data	4 (25)	3 (18.8)	7 (21.9)	

Note. CHM Chinese herbal medicine, TCM traditional Chinese medicine, ECOG Eastern Cooperative Oncology Group, N/A not applicable, M0 metastasis not spread, Mx metastasis is not detectable, IDC invasive ductal carcinoma, LCIS lobular carcinoma in situ

Blood profile

CHM is believed to alter immune function. A number of studies have shown positive results in the immune-modulating effect of CHM [7, 18, 22, 43]. However, there was no significant difference in comparing the chemo-toxicities in anaemia, neutropenia after sixth cycle of chemotherapy in our study, and some other clinical trials have seen similar results [28]. Efficacy of CHM may be reduced when essential criteria are not met, which were the limitation of this study such as limited herbal power selection and herbs pairing raton etc.

This study is an observational study. It has adhered to the traditional practice of CHM, both in terms of individualisation and variation over time. One point of view has argued that the lack of effectiveness in clinical outcomes could merely be a reflection of the herbalist's ability in treating patients. Therefore, the result is that the effectiveness of the treatment always depends on the ability of the herbalists in capturing patients' disease and syndromes progress, and their prescribing formula to their patients. However, the execution of the practice in this study was a reasonable representation of the actual TCM practice in real-life situations, which has been proven by a 14-week follow-up of a clinical trial that continued improvement only in patients with individualised CHM formulations after completion of their treatment, compared with those who received standardised CHM formulations [3].

HRQOL EORTC QLQ-C30

The results of this study are consistent with those of other studies in which CAM users reported that they scored lower in QOL because they were more likely to report their negative feelings and symptoms than those non-users. Moreover, the use of CAM was associated with depression, fear of cancer recurrence, poorer QOL, and more physical symptoms [4, 26]. These may increase the possibility that patients become more likely to use CAM in response to their psychological symptom or lower QOL [4, 12]. These could be some of the reasons that the CHM group in this study had poorer baseline scores compared with the non-CHM group. It is also possible that this might be related the convenience sampling used in selecting the participants. Patients who were willing to participate in this study were given the freedom to choose whether to be in the CHM group or in the non-CHM group. Therefore, it could be that patients with a better cognitive function are more inclined towards the non-CHM group because they have better emotional and psychological adaptation towards their disease progression.

There were no significant differences in the scores of the EORTC-C30 between CHM and non-CHM groups, neither in the raw scores nor in any other clinically significant changes (anchor-based and distribution-based) at the end of the study. This might be due to the small sample size of this study.

However, a number of studies have shown that CHM significantly improved QOL in patients with CHM. Guo et al. (2011) showed that non-small-cell lung cancer patients had scored better in total QOL, physical function, fatigue, nausea and vomiting, pain, and loss of appetite when CHM was integrated with platinum-based chemotherapy regimen [15].

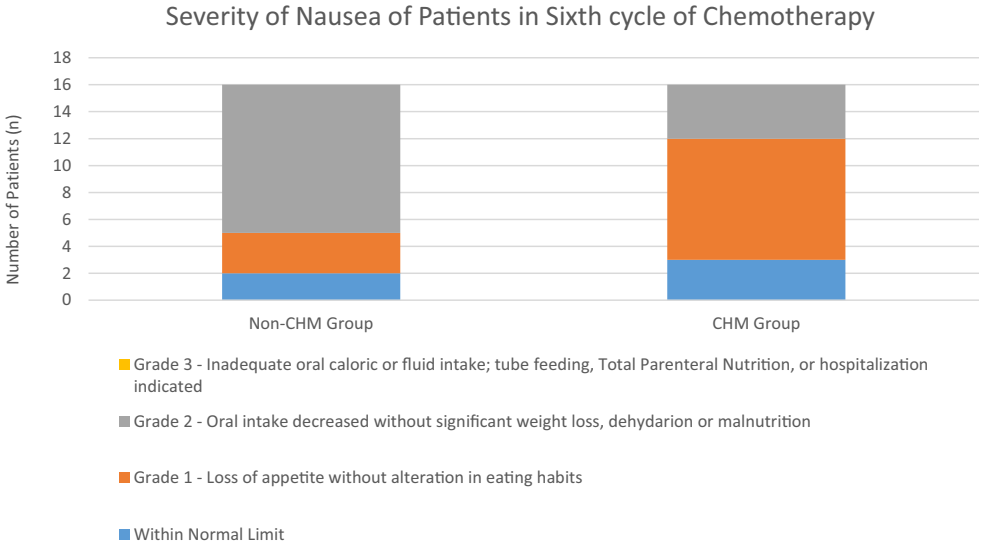

Fig. 1 Severity of nausea of patients in sixth cycle of chemotherapy ($p = 0.04$)

Adverse effects of Chinese herbal medicine

No adverse effects of CHM were reported during the study. However, it must still be considered as an area of potential bias due to the positive impressions of the patients and doctors involved in the study [25, 34], and to the difficulties in identifying the adverse effects which require special training or experience.

Study limitation

The CHM group received CHM medicines, which are in powder forms twice a day based on a formula provided by a CHM practitioner in KBH. The CHM single herbs powder selection was based on the traditionally known medicinal properties of the individual herbs together with the experience of the practitioner. In other words, there was no guideline in CHM formula prescription. Therefore, the effectiveness of CHM treatment may be affected by CHM practitioners' knowledge and experience.

This study is an observational study, and the source of herbal powder is one of the study limitations. The batch of CHM powders was not standardised, and the concentration of the active ingredients in CHM powder form was unknown. Theoretically, each batch of herbs should be properly identified botanically trained personnel based on their morphology, and on microscopic examination. In addition to the identification of the plant material, the adherence of the limits of contamination of the source of CHM powder by heavy metals and microorganism are equally important. The safety of the CHM powder has been assured by the pharmacist-in-charge by sending samples randomly to the National Chemistry Centre for heavy metal tests and microorganism tests. However, the concentration and efficacy of the CHM granules were not tested and remained unknown. Therefore, an assumption

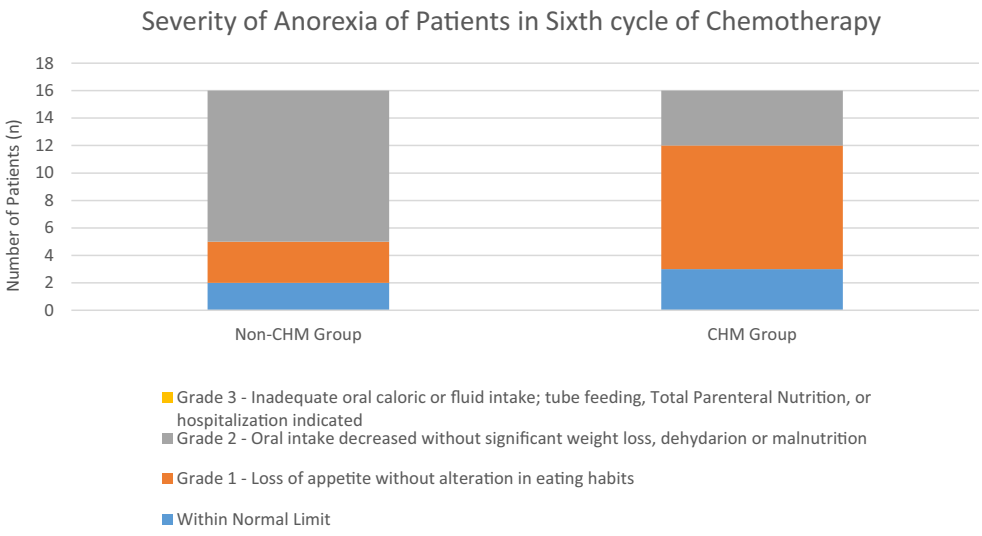

Fig. 2 Severity of anorexia of patients in sixth cycle of chemotherapy ($p = 0.005$)

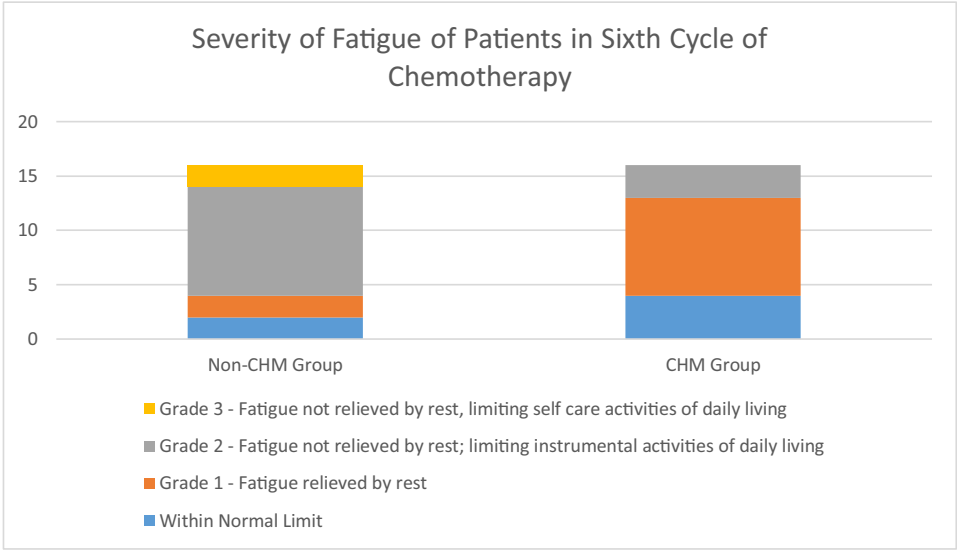

Fig. 3 Severity of fatigue of patients in sixth cycle of chemotherapy ($p = 0.012$)

was made that the qualities of the herbal source were equally good and have been duly standardised.

The pairing of herbs, compatibility, and incompatibility are the foundation of CHM prescription efficacy. Trained CHM practitioners prescribe CHM formulations in order to enhance the therapeutic effects and at the same time to counteract the toxicities or adverse effect of the herbs [24]. The rationale of the herb pair has been proven by modern biomedical research. The pharmacological activity could enhance the solubility of active components in the mixed preparation [14].

In addition to the pairing of herbs, efficacy of the CHM may also be affected by the pairing ratio, as has been proven by previous studies. For instance, it has been shown that some formulations had strongest activities at a certain ratio and no efficacy when out of ratio [11, 42]. The formula used for the CHM group in KBH consisted of a combination of a number of single herbs concentrated granules in 2-g sachets. Patients do the reconstitution of the herbs granules themselves before their administration in 1:1 ratio, respectively. Thus, interactions amongst the bioactive constituents of the combination of herbal granules come into question that the reforming process might lose advantages of the traditional herbal decoction, which are limited not only in pharmacokinetic but also in pharmacodynamics. As a result, there is no definitive conclusion whether the effectiveness of CHM granules is equivalent to the effectiveness of the CHM decoction. Thus, the clinical therapeutic effect cannot be ensured.

Limited choices of the herbs in the T&CM unit may be one of the limitations in the efficacy of patients' prescriptions. There are only 81 types of herbal granules in TCM unit compared with 300 types of commonly used herbs in daily prescribing. The limited choice of herbs and limited herbs combination may reduce the efficacy of CHM treatment.

Patient-reported outcomes of the chemotherapy-induced toxicity were made through phone calls on the third day after

Table 3 Baseline blood profile of the respondents for CHM and non-CHM group

	n	CHM mean (± SD)	Non-CHM mean (± SD)	*p* value
Haemoglobin (g/dL)	16	12.54(1.03)	12.98(1.18)	0.7
White blood cell (×10e9/L)	16	6.30(2.01)	7.15(1.69)	0.8
Platelet (×10e9/L)	16	256.88(63.02)	261.32(61.60)	0.9
Neutrocyte percentage (%)	16	60.14(7.61)	55.91(7.58)	1.0
Bilirubin (g/L)	16	10.78 (5.27)	11.28 (5.11)	0.8
Alkaline phosphatase (U/L)	16	75.44 (27.43)	72.00 (17.77)	0.1
Alanine transaminase (U/L)	16	21.79 (11.54)	27.76 (21.80)	0.3
Creatinine (μmol/L)	16	68.00 (10.97)	67.70 (16.63)	0.6
Natrium level (mmol/L)	16	137.19 (8.80)	136.25 (3.84)	0.4
Potassium level (mmol/L)	16	4.21 (0.43)	4.04 (0.35)	0.7
Absolute neutrophil count	16	3.81 (1.45)	3.92 (1.14)	0.5

every cycle of chemotherapy. The reliability of the assessment may be questionable because recall bias may also be inadvertent, where patients may not remember the number of episode of their adverse effects. Paddilla et al. (1983) indicated that results of patients' symptoms or QOL assessment have the highest reliability coefficients within 1 to 2 hours and have the next highest reliability of coefficients within 24 to 48 hours. Another potential limitation is the study's reliance on patients' self-reported behaviours. Thus, patients' self-reported behaviours might have been influenced by their treatment perception and attitudes. Any improvement amongst patients taking CHM might be due to a "placebo" effect as most of the subjects believed that CHM would be beneficial.

Conclusion

In summary, this study found that CHM group had better fatigue, anorexia, and nausea profile in the sixth cycle of chemotherapy. There was no significant difference in HRQOL of CHM group and non-CHM group or amongst those who delayed the completion of chemotherapy. Although there were no adverse effects reported during the study, patients and healthcare providers should be aware of the potential interactions of CHM and chemotherapy agents. At the same time, patients should be aware of the potential benefits of CHM for cancer treatment, whilst healthcare providers should play their role in the rational use of CHM.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Appendix

List of Stocked Herbs

Morinda officinalis; Herba Hedyotis Diffusae; Bombyx Batryticatus; Rhizoma Imperatae; Rhizoma Atractylodis Macrocephalae; Herba Scutellariae Barbatae; Bulbus Fritillariae; Radix Bupleuri; Semen Arecae Praeparata; Pericarpium Citri Reticulatae; Bulbus Fritillariae Cirrhosae; Radix Et Rhizoma Rhei; Radix Salviae Liguliobae; Radix Angelicae Sinensis; Radix Codonopsis Pilosulae; Cortex Lycii Radicis; Cortex Eucommiae; Rhizoma Curcumae; Rhizoma Pinelliae Preparata; Poria; Radix Glycyrrhizae; Fructus Lycii; Fructus Setariae Germinatus; Radix Polygoni Multiflori; Flos Carthami; Rhizoma Polygonati; Rhizoma Coptidis; Radix Astragali; Radix Scutellariae; Caulis Millettiae; Flos Lonicerae; Flos Chrysanthemi; Radix Sophorae Flavescentis; Semen Armeniacae Amarum; Fructus Hordei Germinatus; Fructus Ligustri Lucidi; Radix Ginseng; Radix Notoginseng; Fructus Mori; Radix Sophorae Tonkinensis; Rhizoma Dioscoreae; Radix Rehmanniae Praeparata; Semen Ziziphi Spinosae; Radix Pseudostellariae; Fructus Schisandrae; Radix Panacis Quinquefolii; Spica Prunellae; Herba; Agrimoniae; Rhizoma Cyperi; Radix Scrophulariae; Herba Leonuri; Semen Coicis; Herba Artemisiae Scopariae; Rhizoma Polygonati Odorati; Rhizoma Alismatis; Rhizoma Anemarrhenae; Fructus Aurantii; Polyporus Umbellatus; Radix Paeoniae Alba; Herba Taraxaci.

Rhizoma Bistortae; Radix Paeoniae Rubra; Semen Phaseoli; Radix Dipsaci; Cortex Moutan; Fructus Trichosanthis; Radix Ophiopogonis; Radix Platycodi; Bulbus Allii Macrostemi; Stamen Nelumbinis; Herba Eupatorii; Folium Eriobotryae; Semen Persicae; Semen Cuseutae; Semen Cuseutae; Fructus Amomi; Fructus Corni; Radix Curcumae; Herba Violae; Radix Glehniae; Herba Epimedii; Rhizoma Acori Talarinowii.

References

1. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JC (1993) The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst 85:365–376
2. Adams M, Jewell AP (2007) The use of complementary and alternative medicine by cancer patients. Int Semin Surg Oncol 4:7
3. Bensoussan A, Talley NJ, Hing M, Menzies R, Guo A, Ngu M (1998) Treatment of irritable bowel syndrome with Chinese herbal medicine: a randomized controlled trial. JAMA 280:1585–1589
4. Burstein HJ, Gelber S, Guadagnoli E, Weeks JC (1999) Use of alternative medicine by women with early-stage breast cancer. N Engl J Med 340:7
5. Chan KKL, YAO TJ, Jones B, Zhao JF, Ma FK, Leung CY, Lau SK, Yip MW, Ngan HYS (2011) 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. Ann Oncol 22:9
6. Chao L-F, Zhang AL, Liu H-E, Cheng M-h, Lam H-B, Lo SK (2009) The efficacy of acupoint stimulation for the management of therapy-related adverse events in patients with breast cancer: a systematic review. Breast Cancer Res Treat 118:255–267
7. Chen S, Flower A, Ritchie A, Liu J, Molassiotis A, Yu H, George L (2010) Oral Chinese herbal medicine (CHM) as an adjuvant treatment during chemotherapy for non-small cell lung cancer: a systematic review. Lung Cancer 68:8
8. Cochrane S, Smith CA, Possamai-Inesedy A, Bensoussan A (2014) Acupuncture and women's health: an overview of the role of acupuncture and its clinical management in women's reproductive health. Int J Women's Health 6:313–325

9. Cui Y, Shu X-O, Gao Y, Wen W, Ruan Z-X, Jin F, Zheng W (2004) Use of complementary and alternative medicine by Chinese women with breast cancer. Breast Cancer Res Treat 85:263–270
10. Damery S, Gratus C, Grieve R, Warmington S, Jones J, Routledge P, Greenield S, Dowswell G, Sherriff J, Wilson S (2011) The use of herbal medicines by people with cancer: a cross-sectional survey. Br J Cancer 104:7
11. Dong TTX, Zhao KJ, Gao QT, Ji ZN, Zhu TT, Li J, Duan R, Cheung AWH, Tsim KWK (2006) Chemical and biological assessment of a Chinese herbal decoction containing *Radix astragali* and *Radix angelicae sinensis*: determination of drug ratio in having optimized properties. J Agric Food Chem 54:2767–2774
12. Downer SM, Cody MM, Cluskey PM, Arnott SJ, Lister TA, Slevin ML (1994) Pursuit and practice of complementary therapies by cancer patients receiving conventional treatment. BMJ 309:4
13. EORTC (2001) EORTC QLQ-C30 scoring manual. In: Editor (ed)^(eds) Book EORTC QLQ-C30 scoring manual. European Organisation for Research and Treatment of Cancer, Brussels 2001, City, pp 78
14. Gao Y, Chen Y (2000) Advances in the study of the effects of danggui buxue decoction and its modified recipes on immunity and hematopoietic function. Zhong Yao Cai 23:177–180
15. Guo L, Bai S-P, Zhao L, Wang X-H (2011) Astragalus polysaccharide injection integrated with vinorelbine and cisplatin for patients wit advanced non-small cell lung cancer: effects on quality of life and survival. Med Oncol 29:1656-62
16. Hasan SS, Ahmed SI, Bukhari NI, Loon WCW (2009) Use of complementary and alternative medicine among patients with chronic diseases at outpatient clinics. Complement Ther Clin Pract 15:152–157
17. Hisham AN, Yip C-H (2004) Overview of breast Cancer in Malaysian women: a problem with late diagnosis. Asian J Surg 27:130–133
18. Huang G-C, Wu L-S, Chen L-G, Yang L-L, Wang C-C (2007) Immuno-enhancement effects of Huang Qi Liu Yi Tang in a murine model of cyclophosphamide-induced leucopenia. J Ethnopharmacol 109:229–235
19. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D (2011) Global cancer statistics. CA Cancer J Clin 61:69–90
20. Lall R, Mistry D, Bridle C, Lamb SE (2012) Telephone interviews can be used to collect follow-up data subsequent to no response to postal questionnaires in clinical trials. J Clin Epidemiol 65:90–99
21. Lee JJ, Lee JJ (2010) A phase II study of an herbal decoction that includes Astragali Radix for cancer-associated anorexia in patients with advanced cancer. Integr Cancer Ther 9:8
22. Li P, Qi L-W, Liu EH, Zhou J-L, Wen X-D (2008) Analysis of Chinese herbal medicines with holistic approaches and integrated evaluation models. TrAC Trends Anal Chem 27:66–77
23. Li SG, Chen HY, Ou-Yang CS, Wang XX, Yang ZY (2013) The efficacy of chinese herbal medicine as an adjunctive therapy for advanced non-small cell lung cancer: a systematic review and meta-analysis. PLoS One 8(2):e57604
24. Li X-J, Zhang H-Y (2008) Synergy in natural medicines: implications for drug discovery. Trends Pharmacol Sci 29:331–332
25. MacLennan AH, Wilson DH, Tailor AW (2002) The escalating cost and prevalence of alternative medicine. Prev Med 35:166–173
26. Maskarinac G, Shimmy DM, Kakai H, Gouty CC (2000) Ethnic difference in complementary and alternative medicine use among cancer patients. J Altern Complement Med 6:8
27. Maskarinec G, Shumay DM, Kakai H, G CC (2000) Ethinic differences in complementary and alternative medicine use among cancer patients. J Altern Complement Med 6:8
28. Mok TSK, Yeo W, Johnson PJ, Hui P, Ho WM, Lam KC, Xu M, Chak K, Chan A, Wong H, Mo F, Zee B (2007) A double-blind placebo-controlled randomized study of Chinese herbal medicine as complementary therapy for reduction of chemotherapy-induced toxicity. Ann Oncol 18:768–774
29. Molassiotis A, Fernadez-Ortega P, Pud D, Ozden G, Scott JA, Panteli V, Margulies A, Browall M, Magri M, Selvekerova S, Madsen E, Milovics L, Bruyns I, Gudmunsdottir G, Hummerston S, Ahmad AMA, Platin N, Kearney N, Patiraki E (2005) Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncol 16:9
30. Naranjo CA, Usoa Busto M, Sellers E, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 30:7
31. Navo MA, Phan J, GVaughan C, Plalmer JL, Michaud L, Jones KI, Bodurka DG, Basen-Engquist K, Hortobogyi GN, Kavanagh JJ, Smith JA (2004) An assessment of the utilization of complementary and alternative medication in women with gynecologic or breast malignancies. J Clin Oncol 22:7
32. National Institutes of Health NCI (2009) Common Terminology Criteria for Adverse Events (CTCAE)V..4.0. p.190
33. Norsa'adah B, Rampal KG, Rahmah MA, Naing NN, Biswal BM (2011) Diagnosis delay of breast cancer and its associated factors in Malaysian women. BMC Cancer 11:8
34. Oh B, Butow P, Mullan B, Beale P, Pavlakis N, Rosenthal D, Clarke S (2010) The use and perceived benefits resulting from the use of complementary and alternative medicine by cancer patients in Australia. Asia Pac J Clin Oncol 6:8
35. Reid K (2015) Chinese herbal medicine for female infertility: an updated meta-analysis complementary therapies in. Medicine 23:13
36. Richardson MA, Sanders T, Lynn Palmer J, Greisinger A, Eva Singletary S (2000) Complementary/alternative medicine use in a comprehensive cancer center and the implications for oncology. J Clin Oncol 18:10
37. Scott NW, Fayers P, Aaronson NK, Bottomley A, de Graeff A, Groenvold M, Gundy C, Koller M, Petersen MA, Sprangers MA (2008) EORTC QLQ-C30 reference values. In: Editor (ed)^(eds) Book EORTC QLQ-C30 Reference Values. EORTC, City
38. Shih V, Chiang JYL, Chan A (2009) Complementary and alternative medicine (CAM) usage in Singaporean adult cancer patients. Ann Oncol 20:752–757
39. Siti ZM, Tahir A, Farah AI, Fazlin SMA, Sondi S, Azman AH, Maimunah AH, Haniza MA, Siti Haslinda MD, Zulkarnain AK, Zakiah I, Zaleha WCW (2009) Use of traditional and complementary medicine in Malaysia: a baseline study. Complement Ther Med 17:292–299
40. Xu L, Li H, Xu Z, Wang Z, Liu L, Tian J, Sun J, Zhou L, Yao Y, Jiao L, Su W, guo H, Chen P, Liu J (2012) Multi-center randomized double-blind controlled clinical study of chemotherapy combined with or without traditional Chinese medicine on quality of life of postoperative non-small cell lung cancer patients. BMC Complement Altern Med 12:6
41. Zhang W, Leonard T, Bath-Hextall FJ, Chambers C, Lee C, Humphreys R, Williams HC (2004) Chinese herbal medicine for atopic eczema. Cochrane Database Syst Rev 18:4
42. Zhao FR, Mao HP, Zhang H, Hu LM, Wang H, Wang YF, Yanagihara N, Gao XM (2010) Antagonistic effects of two herbs in Zuojin Wan, a traditional Chinese medicine formula, on catecholamine secretion in bovine adrenal medullary cells. Phytomedicine 17:659–668
43. Zhuang S-R, Chen S-L, Tsai J-H, Huang C-C, Wu T-C, Liu W-S, Tseng H-C, Lee H-S, Huang M-C, Shane G-T, Yang C-H, Cheng S-Y, Yan Y-Y, Wang C-K (2009) Effect of citronellol and the Chinese medical herb complex on cellular immunity of cancer patients receiving chemotherapy/ radiotherapy. Phytother Res 23:6