Complementary Therapies in Medicine (2015) 23, 309–317

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevierhealth.com/journals/ctim

Influence of adjunctive classical homeopathy on global health status and subjective wellbeing in cancer patients — A pragmatic randomized controlled trial☆

Michael Frass[a,b], Helmut Friehs[b], Christiane Thallinger[a], Narinderjit Kaur Sohal[a], Christine Marosi[a], Ilse Muchitsch[c], Katharina Gaertner[a], Andreas Gleiss[d], Ernst Schuster[d], Menachem Oberbaum[e,*]

[a] *Medical University of Vienna, Department of Medicine I, Clinical Division of Oncology, Waehringer Guertel 18-20, 1090 Vienna, Austria*
[b] *WissHom (Scientific Society for Homeopathy), Köthen, Germany*
[c] *Austrian Chamber of Pharmacists, Department Vienna, HomResearch, Interdisciplinary Homeopathic Research Group, Vienna, Austria*
[d] *Medical University of Vienna, Center for Medical Statistics, Informatics and Intelligent Systems, Vienna, Austria*
[e] *Shaare Zedek Medical Center, The Center for Integrative Complementary Medicine, Jerusalem, Israel*
Available online 23 March 2015

KEYWORDS
Cancer;
Homeopathy;
Additive homeopathy;
Global health status;
Subjective well being

Summary
Objectives: The use of complementary and alternative medicine has increased over the past decade. The aim of this study was to evaluate whether homeopathy influenced global health status and subjective wellbeing when used as an adjunct to conventional cancer therapy.
Design: In this pragmatic randomized controlled trial, 410 patients, who were treated by standard anti-neoplastic therapy, were randomized to receive or not receive classical homeopathic adjunctive therapy in addition to standard therapy. The study took place at the Medical University Vienna, Department of Medicine I, Clinical Division of Oncology.

☆ Trial Registration: ClinicalTrials.gov: NCT00861432.

* Corresponding author at: Shaare Zedek Medical Center, 12 Shmu'el Bait Street, 91031 Jerusalem, Israel. Tel.: +972 2 6666395; fax: +972 2 6666975.
E-mail addresses: michael.frass@meduniwien.ac.at (M. Frass), helmut.friehs@gmx.net (H. Friehs), christiane.thallinger@meduniwien.ac.at (C. Thallinger), narinderjit.sohal@meduniwien.ac.at (N.K. Sohal), christine.marosi@meduniwien.ac.at (C. Marosi), ilse.muchitsch@chello.at (I. Muchitsch), katha_gh@web.de (K. Gaertner), andreas.gleiss@meduniwien.ac.at (A. Gleiss), ernst.schuster@meduniwien.ac.at (E. Schuster), oberbaum@netvision.net.il, oberbaum@szmc.org.il (M. Oberbaum).

http://dx.doi.org/10.1016/j.ctim.2015.03.004

Main outcome measures: The main outcome measures were global health status and subjective wellbeing as assessed by the patients. At each of three visits (one baseline, two follow-up visits), patients filled in two different questionnaires.
Results: 373 patients yielded at least one of three measurements. The improvement of global health status between visits 1 and 3 was significantly stronger in the homeopathy group by 7.7 (95% CI 2.3—13.0, $p = 0.005$) when compared with the control group. A significant group difference was also observed with respect to subjective wellbeing by 14.7 (95% CI 8.5—21.0, $p < 0.001$) in favor of the homeopathic as compared with the control group. Control patients showed a significant improvement only in subjective wellbeing between their first and third visits.
Conclusion: Results suggest that the global health status and subjective wellbeing of cancer patients improve significantly when adjunct classical homeopathic treatment is administered in addition to conventional therapy.

The use of complementary and alternative medicine (CAM), such as herbal, vitamin and nutritional supplements, has increased over the past decade.[1] Various CAM techniques are used by a substantial percentage of patients attempting to ameliorate treatment outcome achieved by conventional therapies. 20—60% of patients in the United States use some form of CAM in various practice settings, with an estimated 16—20% using CAM along with prescribed medication.[2—4] In Austria, 27% of cancer patients (33% female vs. 20% male) use interventions from the broad CAM category.[5] Their administration is widely proposed by general practitioners (44%) or at the patients' own initiative (39%), but very rarely (4%) recommended by the oncologist. Using a detailed interview, the authors show that understanding of CAM methods varies widely.[5] This is not surprising, as complementary medicine includes a broad range of options, from intake of herbal preparations, vitamins and extracts from various natural sources to various religious and spiritual practices. Similar to allopathic medicine, further study is needed to prove that CAM therapies are effective. This is a major concern because patients do not routinely report use of CAM when providing a medication history.[6,7] This observation is complicated by the fact that many oncology patients use several complementary techniques together with their conventional treatment. One example: in a phase I clinical study of 309 patients, 162 (52%) used one or more CAM methods.[8] This rising interest in CAM has been acknowledged by the medical community,[9] with homeopathy, in particular, increasingly used by cancer patients.[10,11]

The aim of this prospective, controlled study was to evaluate whether adjunctive homeopathic treatment has any influence on global health status and subjective wellbeing in patients with various types of cancer. Homeopathy, one of the most popular CAM forms, is based on the 'Law of Similars', which determines that substances causing symptoms in healthy individuals can be used to stimulate healing in patients who have similar symptoms due to their illness.[12] The remedies are produced by serial dilution and vigorous shaking (called succussion) between every dilution. In classical homeopathy, treatment consists of two main elements: taking the individual case history and prescribing individually selected homeopathic medicines, which correspond to the sum of symptoms presented by the patient. The purpose of the homeopathic case history is to ascertain the totality of signs and symptoms of the patient, enabling the selection of an individualized homeopathic medicine based on the broad themes and idiosyncratic characteristics elicited from the totality of presenting symptoms physical, mental and emotional.[12] Classical homeopaths generally use one remedy at a time, usually highly diluted and agitated and in rare repetitions only rarely combining two or more remedies.

In this study, we focused on the homeopathic method. We used standardized questionnaires to assess global health status as well as subjective wellbeing. The study was not designed to evaluate the effect of specific homeopathic remedies used for specific symptoms, such as vomiting and nausea.

Patients and methods

Study design

The study was approved by the Ethical Committee of the Medical University of Vienna on November 4, 2008; # 513/2008. Included were all patients over 18 years of age prior to their first conventional treatment (chemotherapy, radiation therapy, surgical therapy) who signed an informed consent form. The only exclusion criteria were inability to comply with the study protocol, and the mental inability to fill out the questionnaires. On their first visit, patients were told by an administrative staff member about the availability of a study exploring the effect of additive homeopathy on global health status and subjective wellbeing, and were given a patient's information sheet. Once written informed consent was given, eligible patients were randomized to receive standard anti-cancer care (control group), or standard anti-cancer care together with adjunctive homeopathic therapy (homeopathy group).

The random allocation was made by a computer-generated code using sequentially numbered containers. The random allocation sequence (Microsoft Excel) was generated by an individual uninvolved in the study, and study participants were assigned to the groups according to the randomization list. The homeopathy group received individually tailored homeopathic treatment daily, according to the guidelines described by Hahnemann,[12] using the Complete Repertory,[13] Kent's Materia Medica[14] and the Pocket Manual

of Homeopathic Materia Medica & Repertory of William Boericke.[15] Classical homeopathic treatment requires selection of one homeopathic medicine (remedy) at a time for each individual, based on the broad themes and idiosyncratic characteristics elicited from the totality of presenting symptoms —physical, mental and emotional. Homeopathy is defined by the Law of Similars, which means that symptoms which appear after intake of a certain remedy in healthy persons may heal a person suffering from similar symptoms (''Like cures like''). A detailed clinical history is recorded by the homeopath, relying mainly on the symptoms described by the patient. The symptoms are then listed and repertorized. Participation in the study required three visits. Patients were prescribed one homeopathic medicine at each visit, but treatment could be changed at any clinic attendance. A single homeopath (MF) with forty years' experience as a classical homeopath, holding a diploma from the Austrian Medical Chamber and training at the Austrian Medical Association of Classical Homeopathy, consulted and prescribed the remedies. The first visit was 60 min long, and the follow-ups were 30 min each. Remedies were taken daily. Apart from the initial assessment for homeopathic treatment, conventional medical attention regarding length and frequency of medical contacts was identical in both study groups. All patients — both control and treatment groups — were seen in the same clinic, for both their conventional and study treatment. Patients in both groups filled out the questionnaires in this same clinic. Those in the control group received similar assistance and instructions concerning the questionnaires as those in the treatment group.

At all three visits, two different questionnaires were filled out by the study subjects. Time to complete the two questionnaires was an estimated 10 min. The first was the standardized questionnaire of the European Organization for Research and Treatment of Cancer, EORTC-QLQ-C30, focusing on quality of life (QoL) and global health status.[16] The second evaluated subjective wellbeing using a visual analog scale (VAS). The primary outcomes were global health status and subjective wellbeing. Further, several functioning parameters as well as side effects of chemotherapy and radiation such as nausea, appetite loss and constipation were evaluated. The second questionnaire was developed at the Medical University Vienna in Vienna, Austria, and addressed use of other CAM methods, such as acupuncture, mistletoe therapy, herbals, Schuessler cell salts, Bach flowers and vitamins.

Study subjects completed the questionnaires at baseline prior to initial assessment for homeopathic treatment, as well as at the two follow-up visits scheduled at intervals of two months. The prospective endpoint for evaluation of outcomes was therefore four months per patient. Overall, including patient recruitment and recording of outcomes, the study ran from December 2008 to July 2010. The types, frequency and duration of concurrent conventional cancer therapy during the study, as well as the use of other palliative therapies (including antidepressants and corticosteroids) were recorded. Since the study was designed as an open pragmatic trial, we did not use placebo in the control group.

We followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement at the time of protocol development[17] and our reporting followed the RedHOT guidelines (homeopathy specific CONSORT).[18]

Patients

A total 453 patients with malignancies of the breast, lungs, gastrointestinal tract, brain, kidneys and other were screened for enrollment into the study. Of them, 43 did not consent to participation and 410 were, therefore, enrolled (Table 1). All patients received conventional cancer treatment during the trial at the Medical University of Vienna, Department of Medicine I, Clinical Division of Oncology.

Homeopathic treatment

Homeopathic treatment consisted of individualized remedies, prescribed after careful anamnesis and repertorization

Table 1 Patients' characteristics ($n = 373$). All patients had stage III or IV tumors.

	Homeopathy group ($n = 194$)	Control group ($n = 179$)
Age (years, mean ± SD)	55.4 ± 12.5	58.1 ± 11.2
Gender (f, %)	129 (66.5%)	116 (64.8%)
Diagnoses	—	—
Breast cancer	74	79
Hematological cancer	26	19
Gastrointestinal cancer	23	25
Lung cancer	21	22
Renal cell cancer	7	8
Sarcoma	6	1
Brain cancer	7	6
Gynecological cancer	4	1
Other	26	18
Metastatic disease (yes, %)	48 (24.7%)	43 (24.0%)
Chemotherapy (yes, %)	86 (44.3%)	97 (54.2%)
Radiation (yes, %)	25 (12.9%)	33 (18.4%)

following the rules of Samuel Hahnemann, the founder of homeopathy. It was administered daily as oral globules and/or dilutions. The homeopathic remedies were prepared according to the European Pharmacopeia and the Homeopathic Pharmacopeia (HAB 2009; Maria Treu Apotheke, Vienna, Austria). The specific remedy dilutions used were Q-potencies, which patients were advised to take daily. Therapy was started with Q1 and then continued in ascending order with Q2, Q3, etc. In addition, C- and LM-potencies were used, especially for treating side effects of chemo- and radiation therapy. The primary outcome measures were global health status and subjective wellbeing in the homeopathy group.

Statistical analysis

The VAS-values for subjective wellbeing in the second questionnaire were re-scaled 0—100, for the sake of comparison with the EORTC-QLQ-C30 questionnaire. The subscores of the latter were transformed to 0—100, as proposed in the manual.

Sample size calculation

Since to our knowledge the standard deviation of intra-individual differences was not reported in the relevant literature at the time of study planning, the study was designed to detect an effect of one third of a standard deviation (Cohen's $d = 1/3$). Accounting for an expected drop-out rate of up to 25%, a study with 2×191 patients would give 80% power based on a two-sided significance level of 5%. We used the multiple imputation method with 50 simulation runs and constraints between 0 and 100 to impute missing values for the second and the third visits.[19] Due to a non-monotone missing pattern, the Fully Conditional Specification (FCS) method was employed. Each group-specific imputation model comprised age, chemotherapy (yes/no), metastases (yes/no), use of any other CAM treatment (yes/no) as well as available measurements of the respective outcome. Linear imputation models with predictive mean matching were used, other than for dyspnea, insomnia, constipation, appetite loss and diarrhea. For these, logistic imputation models were used since these outcomes have only four categories each.

ANCOVA models were calculated on each of the 50 imputed data sets and results were summarized using Rubin's rules (proc mianalyze of SAS 9.3). In each model, the difference between visits 3 and 1 of the respective outcome was the dependent variable. The independent variables were the randomized group, the respective baseline outcome value (visit 1), age, use of any other CAM treatment, chemotherapy, and metastases (gender and radiation therapy did not prove significant nor to have any relevant impact on the other effect estimates). For an unadjusted estimate of the group difference, the group comparison was adjusted solely for baseline outcome values. For the group-specific changes, least squares estimates (with 95% confidence intervals = 95% CI) depend on the values of the other independent variables in the model. They are therefore evaluated at median values for the covariates and factors and are thus given for typical patients. Group differences of these changes are independent of the co-variables and other factors (there are no interactions in the model due to insignificance) and are presented as least squares means and 95% confidence intervals. *p*-Values for the secondary outcomes (functioning scales and side effects) are corrected for multiple testing using the method of Bonferroni—Holm. *p*-Values of the two primary outcomes were not corrected since the protocol planned reporting of the results of both outcomes independently of their significance.

We performed a sensitivity analysis to investigate the robustness of our assumptions concerning missing values at visits 2 or 3 for the primary outcomes. For this purpose, the imputed values were shifted in favor of the control group by an increasing amount of 5, 10, 15 and 20 units (half of the shift added in the control group and half of it subtracted in the homeopathy group) using the ''mnar'' statement with ''adjust'' option within proc mi of SAS.

All *p*-values are the result of two-sided tests at the (overall) significance level of 0.05. All computations were performed with SAS software 9.4 (SAS Institute Inc., Cary, NC, USA, 2012).

Results

Patients' characteristics (Fig. 1 and Table 1)

The study screened 453 patients, of whom 43 did not consent to participate. The remaining 410 were randomized. After randomization, 37 patients dropped out (16 in the homeopathy group, 21 in control). Thus, 373 patients received allocated treatment (194 in the homeopathy group, and 179 in the control group). 335 patients 173 patients in the adjunctive homeopathy group and 162 controls made the first two of the planned three clinic visits and completed the two sets of questionnaires. 137 patients in the homeopathy group and 145 controls attended the third visit and completed the questionnaires (Fig. 1). Missing values after baseline were imputed (see statistical analysis section), whereas no information was available for the 37 patients who declined after randomization. Our analysis set, therefore, comprises 373 patients. All were treated as intended. Despite randomization, there was a marked difference in age between the two groups (homeopathy: 55.4 ± 12.5 vs. control: 58.1 ± 11.2 years). There were no relevant differences between the groups regarding gender distribution, cancer diagnoses and metastatic disease (Table 1). All patients were in tumor stages III or IV. The type, frequency and duration of concurrent conventional cancer therapy during the study, as well as the degree of use of other palliative therapies, were similar in the two groups, as was the use of antidepressants and corticosteroids. No adverse effects of the homeopathic treatment were observed.

Changes in global health status and subjective wellbeing between the first and third visits

The changes between visits 1 and 3 are summarized in Table 2. In the homeopathy group, a significant improvement in global health status by 10.6 (95% CI 5.3—15.9, $p < 0.001$) and in subjective wellbeing by 20.9 (95% CI 15.6—26.2,

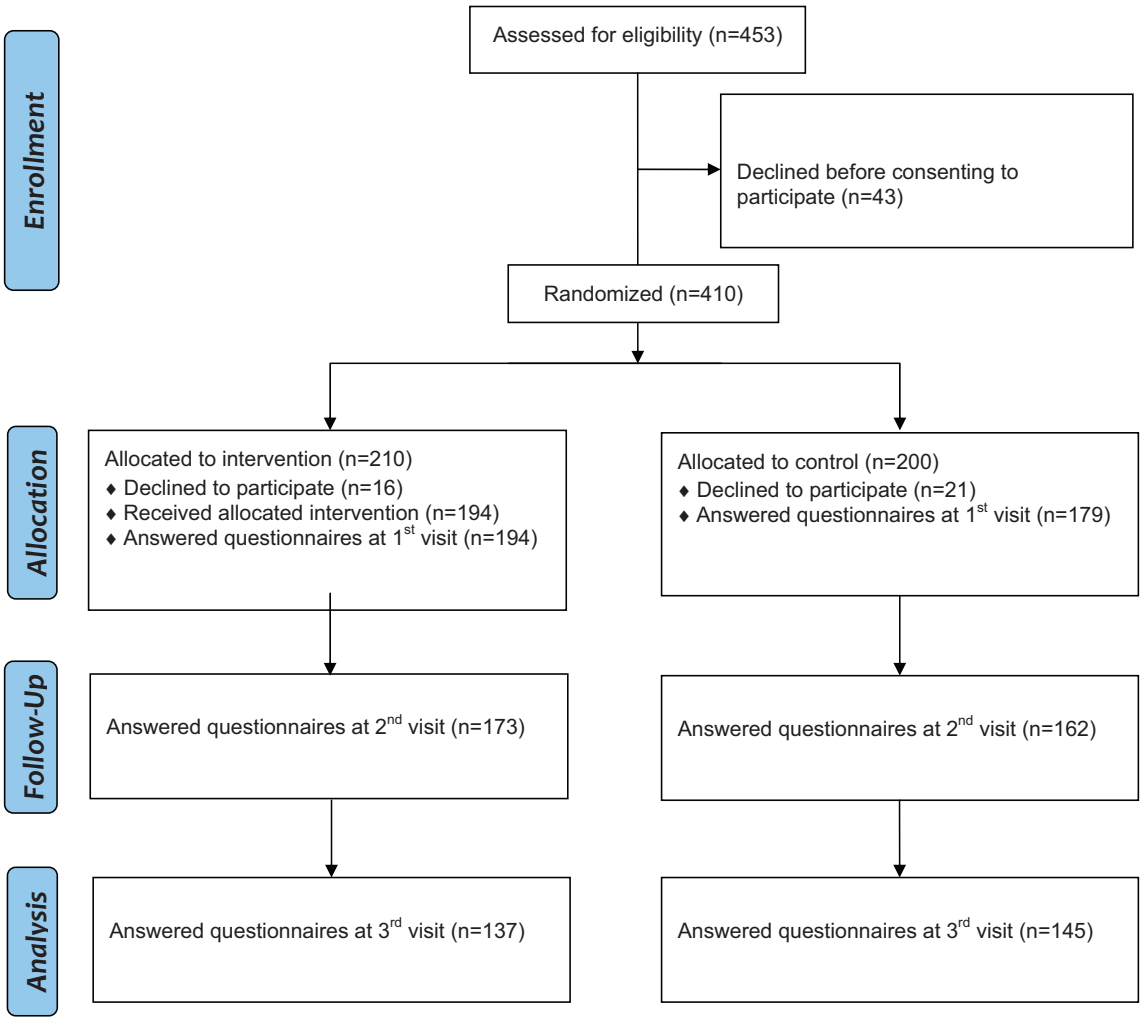

Figure 1 Flow chart.

$p < 0.001$) were detected between the first and third visits (numbers given are for typical patients of median age, median respective baseline value, without chemotherapy and without metastases — see statistics section). In the control group, global health status (3.0; 95% CI 2.5—8.4, $p = 0.288$) did not change significantly between the first and third visits, while subjective wellbeing (6.1; 95% CI 0.3—11.9, $p = 0.039$) changed significantly.

Comparison of Changes in Global Health Status and Subjective Wellbeing between the Adjunctive Homeopathy Group and Control Patients (Table 2 and Fig. 2). The improvement in global health status between visits 1 and 3 was significantly greater in the homeopathy group by 7.7 (95% CI 2.3—13.0, $p = 0.005$). A significant group difference was also observed regarding subjective wellbeing by 14.7 (95% CI 8.5—21.0, $p < 0.001$) in favor of the homeopathic as compared with the control group. The scenarios of our sensitivity analysis show that clinically relevant and statistically significant results are maintained for subjective wellbeing, even for shifts of up to 20 units to the imputed values in favor of the control group (Fig. 2).

Changes in Functioning Scores and Side Effects of Chemotherapy between the First and Third Visits in Adjunctive Homeopathy and Control Patients (Table 2).

In the homeopathy group, a clear improvement in functioning (physical, role, cognitive, social and emotional) was observed, all of it statistically significant after multiplicity correction with the exception of physical functioning. Symptoms of fatigue also decreased significantly ($p \leq 0.001$) while changes in levels of pain, dyspnea, insomnia and appetite loss did not reach statistical significance. Nausea, constipation and diarrhea worsened, albeit not significantly.

In the control group, a significant deterioration of physical functioning was detected. Except for fatigue, all side effects increased, nausea and diarrhea increased even significantly.

Comparison of Changes of Functioning Scores and Side Effects of Chemotherapy between Adjunctive Homeopathy and Control Patients (Table 2)

Compared with control patients, those in the homeopathy group experienced a significant improvement in physical, cognitive, social and emotional functioning. Homeopathic therapy induced significantly less fatigue, pain, dyspnea and appetite loss, compared with the control group. Nausea, insomnia, constipation and diarrhea were also reduced, albeit not significantly.

Table 2 Comparison of first vs. third visits in the group with adjunctive homeopathy and in the group receiving conventional treatment without adjunctive homeopathy (control), and differences of third vs. first visit between the two groups. Least squares means and confidence intervals.

	Homeopathy group				Control group				Homeopathy vs. Control			
	Mean[a]	LCL	UCL	*p*	Mean[a]	LCL	UCL	*p*	Mean	LCL	UCL	*p*
Global health status[b]	10.6	5.3	15.9	<.001*	3.0	−2.5	8.4	0.288	7.7	2.3	13.0	0.005
Subjective wellbeing[b]	20.9	15.6	26.2	<.001*	6.1	0.3	11.9	0.039	14.7	8.5	21.0	<.001
Physical functioning[b]	7.0	1.8	12.2	0.008	−6.5	−11.0	−2.0	0.005*	13.5	8.6	18.4	<.001*
Role functioning[b]	17.0	9.3	24.7	<.001*	8.4	0.6	16.2	0.034	8.6	0.4	16.9	0.040
Cognitive functioning[b]	16.1	10.2	21.9	<.001*	2.4	−3.3	8.1	0.411	13.7	7.7	19.7	<.001*
Social functioning[b]	12.4	5.2	19.6	<.001*	−1.1	−7.8	5.6	0.738	13.6	6.7	20.4	<.001*
Emotional functioning[b]	15.3	8.7	21.8	<.001*	0.9	−5.2	7.1	0.767	14.3	8.0	20.7	<.001*
Fatigue[c]	−19.5	−25.8	−13.1	<.001*	−0.9	−6.9	5.1	0.766	−18.6	−24.7	−12.4	<.001*
Nausea and vomiting[c]	4.0	−1.6	9.7	0.163	8.9	3.9	13.9	<.001*	−4.9	−10.0	0.3	0.066
Pain[c]	−8.5	−15.6	−1.4	0.018	8.4	1.9	15.0	0.011	−17.0	−23.8	−10.1	<.001*
Dyspnea[c]	−9.7	−17.8	−1.6	0.018	2.2	−5.7	10.2	0.580	−11.9	−19.6	−4.3	0.002*
Insomnia[c]	−7.2	−14.7	0.2	0.057	1.0	−6.3	8.3	0.790	−8.2	−15.6	−0.9	0.029
Constipation[c]	5.5	−2.6	13.6	0.184	9.5	2.6	16.5	0.007	−4.1	−11.0	2.9	0.251
Appetite loss[c]	−0.9	−9.1	7.2	0.822	9.0	1.9	16.1	0.013	−9.9	−17.1	−2.7	0.007*
Diarrhea[c]	8.2	0.4	16.1	0.039	12.5	5.2	19.8	<.001*	−4.2	−11.2	2.8	0.235

[a] Least squares group means vary with covariate and factor values; the values reported here are evaluated at a median age of 57, median baseline value of the respective outcome and without chemotherapy, metastases or any other CAM treatment.
[b] Positive change corresponds to improvement.
[c] Negative change corresponds to improvement.
* Significant after adjustment for multiple secondary outcomes using the method of Bonferroni–Holm.
LCL, lower confidence limit; UCL, upper confidence limit; confidence limits are the limits of a 95% confidence interval.

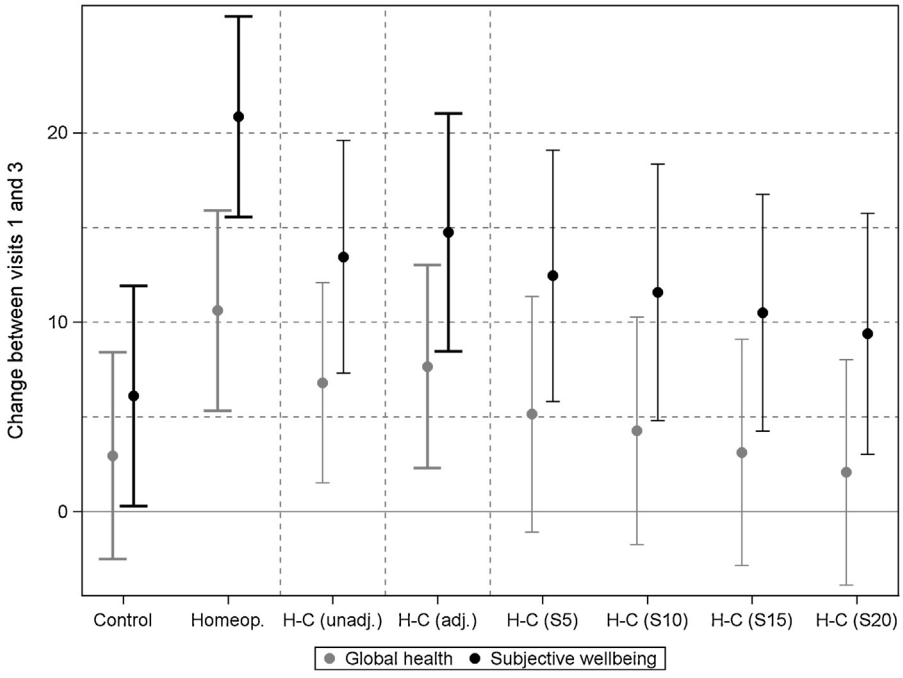

Figure 2 Forest Plot for the change in the primary outcome variables between visits 1 and 3 in homeopathic (H) and control (C) group and for the group difference (H–C) of these changes. Error bars show least squares means and 95% confidence intervals. Unadjusted results of unadjusted analysis (i.e. only adjusted for baseline outcome); adjusted results of the full model; S5, S10, S15, S20: results of sensitivity analysis with shifts of 5, 10, 15 and 20 units added to imputed values in favor of the control group (for details see statistics section). Confidence intervals not including zero indicate statistical significance.

Table 3 Use of other alternative/complementary methods (multiple answers possible, patients reported up to four different methods).

	Homeopathy group ($n = 194$)	Control group ($n = 179$)
Nutritional supplements, such as vitamins	36	37
Bach flowers	35	17
Schuessler cell salts	15	5
Herbals (phytotherapy)	16	14
Mistletoe therapy	10	6
Acupuncture	18	17
Others	61	8
None	106	66

Patients' use of CAM (Table 3)

A marked difference was demonstrated regarding the use of other CAM methods, such as acupuncture, mistletoe therapy, herbals, Schuessler cell salts, Bach flowers and vitamins (Table 3). Control group patients used nutritional supplements such as vitamins, as well as acupuncture, equally often than those in the homeopathy group (Table 3), and they used them throughout the study period. Table 4 lists the homeopathic remedies used most frequently in the homeopathy group. The remedies were prescribed at different dosages (potencies from Q1 to Q30, as well as C6 to C200, and as LM1 to LM30).

Discussion

In this phase II study, we offered cancer patients with different malignancies structured access to homeopathy in addition to their conventional treatment. The study investigated the homeopathic method as such, not specific remedies. In a pragmatic trial, we evaluated the whole ''homeopathic package,'' including exploration and medication. To our knowledge, this is the first prospective randomized controlled phase II study that has evaluated the influence of complementary homeopathic treatment in patients with malignancies treated at the same institution. A non-randomized study was performed by Rostock et al. where treatment of the two groups was administered in four different institutions.[11] Their findings were similar to ours, namely an improved quality of life (QoL) and a tendency to decreased fatigue symptoms.

Table 4 Most frequently used homeopathic remedies.

1	Phosphor	133
2	Sulphur	84
3	Natrium muriaticum	64
4	Lachesis	63
5	Pulsatilla	47
6	Arsenicum album	46
7	Nux vomica	39
8	Calcium carbonicum	38
9	Silicea	27
10	Lycopodium	26
11	Conium	25
12	Mercurius solubilis	25
13	Thuja	19
14	Sepia	17
15	Rhus toxicodendron	16
16	Ignatia	14
17	Kalium muriaticum	12
18	Chininum arsenicosum	11
19	Natrium sulphuricum	11
20	Staphisagria	10

We observed that homeopathy used as a complementary modality to state-of-the-art cancer treatment improved both global health status and subjective well-being, compared with control group patients who did not receive adjunctive homeopathic treatment. The improvement in global health status and subjective wellbeing occurred between the first and third visits in the homeopathy group and was statistically significant. During the same period, patients who received solely state-of-the-art oncologic treatment experienced a markedly lower decrease of global health status and subjective wellbeing, in agreement with recently reported data.[16] Thus, homeopathy patients improved in contrast to control patients. Patients from the adjunctive homeopathy group reported a significantly greater improvement in physical, cognitive, social and emotional functioning, as well as decreased fatigue, pain and appetite loss, compared with control patients. We ruled out the possibility that these improvements were associated with other additional supportive treatments, such as increased use of antidepressants or corticosteroids in the adjunctive homeopathy group, since we found no statistical difference in their use between the two groups.

The factors influencing the increasing use of CAM methods by cancer patients were addressed in a recent study in the context of whether their use may be associated with perceived distress or poor compliance with standard treatment.[20] In this study, the predictors for use of CAM were younger age, progressive cancer and active coping behavior. Surprisingly, use of CAM was not associated with poor compliance regarding conventional medical treatment.

We added a complex homeopathic setting to conventional care and tested it against conventional care alone and found that it improves both wellbeing and QoL. The study was not designed to show which component of homeopathic treatment was effective, only that, from a pragmatic point of view, patients benefit from additional homeopathic treatment.

This study was an 'add-on' trial: the 'standard anticancer care' and all other treatments were the same in both groups, the only difference being addition of classical homeopathic treatment for the patients in the treatment group. In classical homeopathic treatment, other types of intervention (e.g., nutritional supplements and acupuncture) are normally discouraged. On the other hand, as is customary in pragmatic trials, other complementary interventions were not prohibited. Some patients, therefore, used additional CAM techniques. It may be suggested that this could have created additional variability and possible bias. By adding use of other CAM methods to the multi-variable analysis of

the primary outcomes as an additional factor, the treatment effect estimate is adjusted for different use of any other CAM in the two groups. With this being a pragmatic trial, we were interested in the 'net effect' which reflects effectiveness rather than efficacy.[21]

A limitation of the study may be the heterogeneity of cancer entities that it included. There were, however, no significant differences between patients in the two groups regarding gender distribution, cancer diagnosis and metastatic disease. The type, frequency and duration of concurrent conventional cancer therapy during the study were similar in the two groups. Another possible limitation of the study is the high attrition rate which may introduce some bias; to counter this, we employed multiple imputation techniques. A sensitivity analysis showed that, at least for subjective well-being, the results presented prove robust to deviations from the missing at random assumption underlying the multiple imputation method.

The number of patients completing the third set of questionnaires was, however, low, and not for reasons of death or clinically significant deterioration. We have no explanation for the high attrition rate.

Despite randomization, we observed differences between the groups at baseline with respect to the primary outcome measures. ANCOVA models were used to adjust the group comparisons not only for potential confounders such as age or oncological therapy but also for different levels of the outcome measures at the first visit. In this way, potential regression-to-the-mean effects that may be stronger in the group with poorer baseline values were adequately met.[22] We have no explanation as to why the number of patients completing the third set of questionnaires was lower in the homeopathy than in the control group. Another of the study's limitations is that outcome assessment took place on an unblinded basis and that 37 patients quit the study after randomization without even baseline measurements. The reason for declining after randomization was obviously driven either by disappointment at being allocated to the undesired group or by late awareness of the additional pressure of homeopathic consultations. Some participants allocated to the control group were resentful or demoralized because they did not receive the homeopathic treatment they had hoped for. Resentful demoralization, however, may actually not have been so great a problem, because only five more patients in the control group declined to participate compared with the homeopathy group.

The study's limitations are those of all pragmatic trials: frequently, treatments with moderate effects may benefit from the lack of blindness and allocation concealment, and patient preferences or beliefs can influence the outcome of the study. This has been shown in empirical studies which demonstrated that trials without or with inappropriate blinding and/or allocation concealment are often (erroneously) more statistically significant than RCTs, which are better controlled.[21,23,24] Whereas a pragmatic trial can shed light on the overall performance of a treatment, it will very often be difficult to identify the specific components (or even biases) that explain this effectiveness.

A further limitation is the absence of a placebo control group. This, however, does not disqualify a study, since many conventional cancer studies are not placebo-controlled.[25,26] To overcome this limitation, we are currently performing a double-blind placebo-controlled study to test whether the results of the present study are reproducible under more stringent conditions with longer follow-up.

The issue of 'equipoise' is often a controversial issue in trials of treatment modalities where patients are likely to have a strong preference for the treatment, which is often applicable in CAM/homeopathy. The concern is that only patients with a weaker preference will be prepared to be included in the trial, with possible negative effects on outcomes as compared with patients seen in routine practice.

Homeopathy is controversial within the medical scientific community, with heated discussion relating mainly to the effectiveness of high potencies. Interestingly, thermoluminescence investigations have shown that high potencies beyond Avogadro's number exhibit physical properties,[27] and a scattering of preclinical trials in homeopathy can already be seen within conventional literature.[28,29] The role of the homeopathic consultation vs. the homeopathic remedy as being the possible main effect of the whole practice of homeopathy must be kept in mind. Discussions about homeopathy often include the role of placebo. This, however, seems to be overemphasized. Hróbjartsson and Gøtzsche have recently conducted a systematic review of clinical trials in which patients were randomly assigned to either placebo or ''no treatment'' groups. The authors found little evidence in general that placebo has powerful clinical effects,[30,31] and its role should thus be reconsidered. The observed beneficial effects of homeopathic adjunctive treatment, the lack of side effects as well as the low cost of homeopathic remedies contrast with other potential medically or financially 'toxic' CAMs, taken without the knowledge of the medical oncologist. The attitude toward CAM was assessed in a study evaluating current knowledge, attitudes and interests of medical students, general physicians and gynecologists.[32] Doctors believed that CAM is most useful in general medicine, supportive oncology, pediatrics, dermatology and gynecology, whereas students believed that dermatology, general medicine, psychiatry and rheumatology offer opportunities.

Our findings may also be important because health-related QoL is regarded as an important end-point in oncological clinical trials. According to the results of our study, QoL may be influenced on an individual level by the described procedure or possibly by other CAM interventions that influence QoL.[33,34] It may be speculated that such interventions could also influence the outcome in one or other treatment branch, resulting in mistaken conclusions about the study drug in question, particularly if there is an imbalance in patient inclusion regarding the patient characteristics mentioned above. It may thus be concluded from the obvious frequency of CAM use by patients as well as from the present data that clinical report forms should include an analysis of CAM use during clinical trials to enable statisticians to accurately analyze study outcome.

Conclusions

The results achieved in some three decades of research into homeopathic cancer treatment do not yet justify use of

homeopathy as an alternative to conventional cancer therapy. On the other hand, there is a growing corpus of evidence indicating that homeopathy may play a significant role in integrative oncology as a supportive therapy. We believe our results bolster this view and suggest that global health status and subjective wellbeing of cancer patients can be significantly improved with homeopathic treatment. Additive homeopathic treatment could therefore be considered a safe and supportive therapy for cancer patients.

Conflict of interest

No competing financial interests exist. No funding had been obtained for this study from any source.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ctim.2015.03.004.

References

1. Navo MA, Phan J, Vaughan C, et al. An assessment of the utilization of complementary and alternative medication in women with gynecologic or breast malignancies. *J Clin Oncol* 2004;**22**:671—7.
2. Eisenberg DM, Davis RB, Ettner SL, et al. Trends in alternative medicine use in the United States, 1990—1997: results of a follow-up national survey. *J Am Med Assoc* 1998;**280**:1569—75.
3. Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. *J Am Med Assoc* 2002;**287**:337—44.
4. Yoon SJ, Horne CH. Herbal products and conventional medicines used by community-residing older women. *J Adv Nurs* 2001;**33**:51—9.
5. Spiegel W, Zidek T, Vutuc C, Maier M, Isak K, Micksche M. Complementary therapies in cancer patients: prevalence and patients motives. *Wien Klin Wochenschr* 2003;**115**:705—9.
6. Harnack LJ, Rydell SA, Stang J. Prevalence of use of herbal products by adults in the Minneapolis/St Paul, Minn, metropolitan area. *Mayo Clin Proc* 2001.
7. Von Gruenigen VE, White LJ, Kirven MS, et al. A comparison of complementary and alternative medicine use by gynecology and gynecologic oncology patients. *Int J Gynecol Cancer* 2001;**11**:205—9.
8. Naing A, Stephen SK, Frenkel M, et al. Prevalence of complementary medicine use in a phase 1 clinical trials program: the MD Anderson Cancer Center Experience. *Cancer* 2011;**117**:5142—50.
9. Levine MN. Conventional and complementary therapies: a tale of two research standards? *J Clin Oncol* 2010;**28**:1979—81.
10. Längler A, Spix C, Edelhäuser F, Kameda G, Kaatsch P, Seifert G. Use of homeopathy in pediatric oncology in Germany. *Evid Based Complement Alternat Med* 2010;**2011**:867151, http://dx.doi.org/10.1155/2011/867151.
11. Rostock M, Naumann J, Guethlin C, Guenther L, Bartsch HH, Walach H. Classical homeopathy in the treatment of cancer patients — a prospective observational study of two independent cohorts. *BMC Cancer* 2011;**17**(11):19, http://dx.doi.org/10.1186/1471-2407-11-19.
12. Hahnemann CFS. *Organon der Heilkunst*. 6th ed. Heidelberg: Haug; 1989.
13. Zandvoort R. *The Complete Repertory. Institute for Research in Homeopathic Information and Symptomatology*. The Netherlands: AJ Leidschendam; 1994—1996.
14. Kent JT. *Lectures on Homeopathic Materia Medica*. Philadelphia, USA: Boericke and Tafel; 1905.
15. Boericke W. *Homeopathic Materia medica with repertory*. 1st ed., 1995 Sittingbourne, Great Britain: Homeopathic Book Service; 1980.
16. Fayers P, Bottomley A. EORTC Quality of Life Group; Quality of Life Unit: Quality of life research within the EORTC-the EORTC QLQ-C30. European Organisation for Research and Treatment of Cancer. *Eur J Cancer* 2002;**38**(Suppl 4):125—33.
17. Chan AW1, Tetzlaff JM, Altman DG, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;**158**:200—7.
18. Dean ME, Coulter MK, Fisher P, et al. Reporting data on homeopathic treatments (RedHot): a supplement to CONSORT. *Homeopathy* 2007;**96**:42—5.
19. Fairclough DL. *Design and analysis of quality of life studies in clinical trials*. Chapman & Hall, CRC; 2002.
20. Molassiotis A, Fernadez-Ortega P, Pud D, et al. Use of complementary and alternative medicine in cancer patients: a European survey. *Ann Oncol* 2005;**16**:655—63.
21. Wood L, Egger M, Gluud LL, et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. *Br Med J* 2008;**336**:601—5.
22. Bonate PL. *Analysis of pretest—posttest designs*. Boca Raton, USA: Chapman & Hall/CRC; 2000.
23. Odgaard-Jensen J, Vist GE, Timmer A, et al. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev* 2011;**4**:MR000012.
24. Pildal J, Hrobjartsson A, Jorgensen KJ, et al. Impact of allocation concealment on conclusions drawn from meta-analyses of randomized trials. *Int J Epidemiol* 2007;**36**:847—57.
25. Bill-Axelson A, Holmberg L, Garmo H, et al. Radical prostatectomy or watchful waiting in early prostate cancer. *N Engl J Med* 2014;**370**:932—42.
26. Bottomley A, Tridello G, Coens C, et al. An international phase 3 trial in head and neck cancer: quality of life and symptom results: EORTC 24954 on behalf of the EORTC Head and Neck and the EORTC Radiation Oncology Group. *Cancer* 2014;**120**:390—8.
27. Rey L. Can low-temperature thermoluminescence cast light on the nature of ultra-high dilutions? *Homeopathy* 2007;**96**:170—4.
28. Pathak S, Multani AS, Banerji P, Banerji P. Ruta 6 selectively induces cell death in brain cancer cells but proliferation in normal peripheral blood lymphocytes: a novel treatment for human brain cancer. *Int J Oncol* 2003;**23**:975—82.
29. Frenkel M, Mishra B, Yang P, et al. Cytotoxic effects of ultra-diluted remedies on breast cancer cells. *Int J Oncol* 2010;**36**:395—403.
30. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;**344**:1594—602 [Review].
31. Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010;**20** (January (1)):CD003974, http://dx.doi.org/10.1002/14651858.CD003974.pub3 [Review].
32. Münstedt K, Harren H, von Georgi R, Hackethal A. Complementary and alternative medicine: comparison of current knowledge, attitudes and interest among German medical students and doctors. *Evid Based Complement Alternat Med* 2008:790951 [Epub 2008 Dec 20].
33. Frenkel M. Homeopathy in cancer care. *Altern Ther Health Med* 2010;**16**:12—6.
34. Montazeri A. Quality of life data as prognostic indicators of survival in cancer patients: an overview of the literature from 1982 to 2008. *Health Qual Life Outcomes* 2009;**7**:102.