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Research paper

Supportive effect of *Viscum album* L. extracts on the sense of coherence in non-metastasized breast cancer patients

Shiao Li Oei[a,1], Anja Thronicke[a,1], Matthias Kröz[a,c,d], Cornelia Herbstreit[e], Friedemann Schad[a,b,*]

[a] Research Institute Havelhöhe, Kladower Damm 221, 14089 Berlin, Germany
[b] Oncological Centre, Hospital Havelhöhe, Kladower Damm 221, 14089 Berlin, Germany
[c] Institute of Social Medicine, Charité 10178 Berlin, Germany
[d] Institute for Integrative Medicine, 58313 Witten/Herdecke, Germany
[e] Breast Cancer Centre Hospital Havelhöhe Kladower Damm 221 14089 Berlin Germany

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ABSTRACT

Introduction: *Viscum album* L. extracts (VA) are frequently used in integrative oncology to enhance health-related quality of life. As a central aspect of well-being is associated with feeling warm or cold the internal coherence scale (ICS) questionnaire including the thermo coherence measurement was utilized.

Methods: A prospective observational longitudinal cohort study was conducted, using data from the Network Oncology clinical registry. Primary non-metastasized breast cancer patients diagnosed in a German certified breast cancer center and treated either with standard anti-hormonal therapy alone (control) or in combination with VA-extracts (VA-group) were included. At first diagnosis, 6 months and 12 months later, the ICS-questionnaire was administered and analysed.

Results: In total, 72 patients (56 control and 16 VA-patients; median age 62.1 years, IQR: 52.3–70.6) were evaluated. 6 months after first diagnosis, only for the VA-group a considerable increase of the total ICS and particularly the thermo coherence score was observed ($p\ (d) < 0.01$). Furthermore, after 12 months in a subgroup of 45 patients, 69% of the VA-group, felt an advancement of warmth, while only 25% of the controls had this feeling. This significant effect remained consistent in a multivariable regression analysis ($p = 0.006$).

Conclusions: Our findings suggest that concomitant VA is positively associated with an impact on the thermo coherence of breast cancer patients and VA-applications might be an option to harmonize discomfort symptoms during anti-cancer therapy. However, results should be interpreted with caution in light of the study´s observational character.

1. Introduction

Health-related quality of life (HRQL) is of growing importance in clinical oncology [1,2]. *Viscum album* L. extracts (VA, mistletoe) are frequently used in integrative oncology to enhance HRQL and to reduce adverse side effects (for review [3,4]). VA-applications are usually well tolerated with few and mild side-effects [5–7]. In patients with pancreatic carcinoma it has been reported that VA-treatment improved HRQL [8] and further studies have articulated the influence of VA therapy on HRQL in cancer patients, especially in breast cancer patients during chemotherapy [9–12]. Despite growing evidence of the benefits in breast cancer patients, further studies are needed to assess effectiveness of add-on VA-therapy.

Numerous questionnaires have been developed, to objectify and standardize HRQL analysis [13]. Established instruments in oncology are e.g. the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 [14] and the functional assessment of cancer therapy (FACT) scale [15]. Antonovsky developed a salutogenic model [16] by introducing the concept of ´sense of coherence´, which addresses general resistance resources in patients. The sense of coherence is a resource that enables people to manage tension in a health promoting manner and as reviewed by Eriksson and Lindstrom [17], has a substantial impact on HRQL. Several studies have articulated the potential relevance of the sense of coherence for cancer patients [18,19]. Therefore, a prognostic tool with a specific 10-item scale of internal coherence (ICS) questionnaire capturing the individual skills of

* Corresponding author at: Gemeinschaftskrankenhaus Havelhöhe, Kladower Damm 221, 14089 Berlin, Germany.
E-mail addresses: shiaoli.oei@havelhoehe.de (S.L. Oei), anja.thronicke@havelhoehe.de (A. Thronicke), matthias.kroez@havelhoehe.de (M. Kröz), cornelia.herbstreit@havelhoehe.de (C. Herbstreit), fschad@havelhoehe.de (F. Schad).
[1] Contributed equally.

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adaption with good to very good reliability was developed and validated [20]. The structure of this ICS-questionnaire enables measuring the total ICS-score as well as factors of inner resilience, inner coherence and thermo coherence [20]. Previously, it was described that this ICS-questionnaire showed a good sensitivity for oncological patients, particularly regarding chemotherapy and add-on VA-therapy [21].

Systemic oncological therapies including anti-hormonal treatments for breast cancer patients are often applied at the cost of numerous side effects which have been shown to impair HRQL [22]. Hormone suppression remains the gold standard for hormone-sensitive breast cancer. However, patients treated with anti-hormonal therapies frequently report side effects including hot flushes [23]. The pathophysiology of hot flushes involves complex interactions and a decline in estrogen has been suggested to cause a change in the thermoregulatory set point in the hypothalamus [24]. An important aspect of well-being is associated with feeling warm or cold, which therefore represents a relevant aspect of HRQL. A thermal dysregulation, such as `feeling cold´, congestive sweating or having hot flushes are often seen in patients with breast cancer affecting their HRQL [25]. Furthermore, subjective thermal comfort plays a critical role in body temperature regulation and reflects the primary stimulus for thermoregulation [26]. The body core predominates in regulation of the autonomic and metabolic responses, whereas the core and skin-surface temperature contribute towards thermal comfort [26]. A thermal dysregulation has been particularly seen in premenopausal breast cancer patients and this can be related to explicitly affecting the HRQL [27]. However, as thermal sensation or comfort is difficult to assess, the ICS-questionnaire is a relevant tool by explicitly considering a score for thermal comfort.

Consequences of anti-hormonal therapy can be the increase of menopausal symptoms including thermal discomfort and hot flushes [28]. In our certified breast cancer center the majority of patients receive anti-hormonal treatments [29]. The key implication of the present observational study was to evaluate the effects of additional VA treatment on the sense of coherence and especially thermo coherence of breast cancer patients receiving standard anti-hormonal treatments. Our objective was to test the hypothesis that breast cancer patients receiving additional VA are better supported in their sense of coherence than patients receiving standard therapy alone.

2. Methods

2.1. Study design and patients

We conducted a non-controlled, non-randomized observational cohort study by analyzing patient registry data (Network Oncology, NO). The NO is a conjoint clinical register of hospitals, practitioners and outpatient centers for the evaluation of integrative oncological therapy concepts in health services research oncology [30]. Oncological patients from whom written informed consent was obtained were included in the NO. In addition to recording clinical parameters, non-pharmacological interventions and VA treatments are documented and surveys of questionnaires on quality of life at different time points are conducted. For the present study, patients with a histologically proven primary diagnosis of non-metastasized breast cancer were included.

2.2. Endpoints

The key element of this study was to evaluate the effect of add-on VA applications on the sense of coherence of non-metastasized breast cancer patients. The primary outcome of the present study was to investigate the increment of thermo coherence in patients treated with anti-hormonal standard therapy combined with VA compared to patients only receiving anti-hormonal standard therapy. The hypothesis, whether breast cancer patients receiving concomitant VA therapy are better supported in their sense of coherence than patients receiving standard therapy alone, was to be tested.

2.3. Data collection

For the present evaluation, similar to that reported previously [29,31], primary non-metastasized breast cancer patients of the NO seen at the certified Breast Cancer Centre Gemeinschaftskrankenhaus Havelhöhe (GKH, Berlin, Germany) between June 2012 and August 2017 were screened. The patients visited the surveillance and study center at 3 time points -visit 1 at first diagnosis (T0), visit 2 at 6 months (T1), and visit 3 at 12 months (T2) after first diagnosis. During these visits they received and pseudonymously answered the ICS-questionnaires. All data reported here are based on retrievable data from the NO registry at cut-off date of August 29, 2017. Patients from which completed ICS-questionnaires at T0 and T1 or all three measured time points were available, were enrolled in the present study. Furthermore, only female primary non-metastasized breast cancer patients aged 33 to 81, receiving anti-hormonal therapy within 6 months after first diagnosis were included. Exclusion criteria were: no written consent, patients treated with chemotherapy or trastuzumab, patients rejecting anti-hormonal therapy, or patients from whom only incomplete questionnaires were available. The number of patients fulfilling all inclusion criteria and completely answering the ICS questionnaire for at least T0 and T1 determined the sample size. Patient-reported outcomes were evaluated by analyzing the ICS-questionnaires in both groups. In addition to the analysis of patient reported outcomes, demographic and medical data (diagnosis, histology, pre-treatment and treatment) of the enrolled patients were retrieved from the NO). Furthermore, application of VA extracts in the context of an integrative oncological setting with start and end dates as well as VA application type was retrieved. To identify influencing factors and to address potential sources of bias an adjusted multivariable linear regression analysis was performed.

2.4. Group allocation

The patients were treated with oncological standard therapy and informed by physicians to make use of receiving add-on VA-therapy. Further inclusion criteria were, following the advice receiving anti-hormonal therapy. The patients were allocated according to their applied therapies. Patients who received anti-hormonal therapy alone within 6 months after first diagnosis were allocated to the “control” group. Patients who received anti-hormonal therapy and add-on VA-applications within 6 months after first diagnosis were allocated to the “VA” group. Applied VA preparations included Abnobaviscum, Helixor, Iscador, and Iscucin VA extracts. VA therapy was applied subcutaneously according to summary of product characteristics. Off-label intravenous application was performed in individual cases. Eligible patients for subgroup analysis were those who completed the ICS questionnaire for T0, T1, and T2.

2.5. Ethics approval and consent to participate

The study complies with the principles laid down in the Declaration of Helsinki. This NO study has been approved by the ethics committee of the Medical Association Berlin (Berlin – Ethik-Kommission der Ärztekammer Berlin). The reference number is Eth-27/10. This study had been retrospectively registered at the WHO approved register German Register for Clinical Trials (Deutsches Register Klinischer Studien, DRKS), trial registration number DRKS00013335 (http://www.drks.de/drks_web/setLocale_EN.do). Written informed consent was obtained from all patients prior to study enrollment.

2.6. ICS-questionnaire

The ICS-questionnaire is a short, highly reliable and valid ten items questionnaire based on a 5-point Likert scale (range: 10 (low ICS) – 50 (high ICS)). (An English version of the ICS-questionnaire can be found in the Supplementary Appendix) The ICS contains two subscales one

with eight items (Inner Coherence and Resilience) and a second subscale (Thermo Coherence) with two items, which has been described earlier [20]. In question 3, "I felt pleasantly warm" the options to select corresponded to score 5 to 1. For measuring the individual feeling of warmth, the individual scores of question 3 were compared (T2 versus T0) during course of time, and classified into "warmer", "equal", or "colder", respectively.

2.7. Statistical analysis

For both groups, baseline characteristics and treatment regimens were compared using the Wilcoxon-Mann-Witney test for categorical and continuous variables. Continuous variables were described as median with interquartile range (IQR); categorical variables were summarized as frequencies and percentages. p-values < 0.05 were considered to be significant. Patients with missing data were not included. Wilcoxon-Mann-Witney, two-sided Student´s t-test, and Pearson`s chi-squares respectively were applied, to detect differences between control and VA-groups. Data distributions were inspected graphically using box-plots and diagrams. All statistical analyses were performed using the software R (R Version 3.1.2 (2014))[32]. For Pearson`s chi-square calculation the basic R-package was used, for Cohens´d analyses in addition the "compute.es" package was used.

To quantify the strength of the relationship for the individual feeling of inner warmth, the individual answer scores of the ICS-question 3 were compared between T0 and T2 and classified into "warmer" = 2, "equal" = 1, or "colder" = 0 respectively. To identify influencing factors and to address potential sources of bias an adjusted multivariable linear regression analysis was performed and potential confounders were addressed. Predicting variables (with regard to T0) were age (in years), body mass index BMI (in classes: normal, overweight, obese), UICC stages (categorical 0, I, II, III), hormonal stage (pre/post-menopausal, *HER2* positive (yes/no).

3. Results

3.1. Patient´s characteristics

In total, 199 non-metastasized breast cancer patients answered the ICS-questionnaires. Complete data were collected for 72 eligible patients receiving anti-hormonal treatment with (n = 16) or without (n = 56) additional VA-therapy (see also study flow chart, Fig. 1). Patients who were not included in our analysis received chemo- or targeted therapy (n = 66), had no anti-hormonal treatments documented in the records (n = 54), or had incomplete data-sets retrievable from the NO-registry (n = 7). Table 1 shows the main characteristics of analyzed patients at baseline. No significant differences between groups with regard to demographic characteristics were seen. The median age was 62 years, the hormonal status of the majority (72%) was post-menopausal. The percentage of patients diagnosed with progesterone receptor positive was significant higher in the control group compared to the VA-group. Patients of the VA-group had a lower mean BMI and were affected by more severe UICC-stages. In Table 2 the interventions which were applied to the patients are listed. No significant differences between groups with regard to interventions were seen. Most patients received surgical interventions (95.8%) and radiations (90.3%). According to advised oncologic therapy, anti-hormonal treatment started in general within 6 months after first diagnosis and was administered with the intention to treat for 5 years. Tamoxifen was the most frequent anti-hormonal therapy, applied to 49 patients (68%). For the 16 patients of the VA-group, VA-therapy started within 6 months after first diagnosis (for details see Table 3). Abnoba extracts were the mistletoe remedies most often prescribed (n = 8), followed by Iscador remedies (n = 6), Helixor applications (n = 4), and Iscucin preparations (n = 2). All 16 patients received subcutaneous VA-applications. Two patients received additionally off-label intravenous VA-injections of which one received as well oral VA-applications.

3.2. ICS evaluation

Completed ICS-questionnaires of 56 control and 16 VA patients were evaluated for T0 and T1. The total- and subscales 'inner resilience and coherence' and 'thermo coherence' were calculated. The mean values and differences between the VA- and control-group were determined for all scales. The comparison of the total ICS- and the thermo coherence score - values for T1 in relation to T0 revealed an increase for both groups during therapy, but more pronounced for the VA-group. At T1, a significant increase of the total ICS was obtained for the VA- versus the control-group. The calculation of the Pearson's Chi-squared test and of Cohens´ d revealed a significant medium effect, d [95%CI] = 0.75 [0.25, 1.26] with p-value(d) < 0.01 for this increase (VA versus control at T1; table in Fig. 3). Even more pronounced were the VA-effects for the thermo coherence (TC). At T0 and T1 the mean values of the thermo coherence for the control were $TC_{T0} = 7.39 \pm 2.04$ and $TC_{T1} = 7.59 \pm 1.94$ respectively, while for the VA-group, the thermo coherence raised substantially (from 7.13 ± 2.03–8.31 ± 1.26). Chi-squared test and Cohens´ d analyses revealed a significant high effect, d [95%CI] = 0.78 [-0.01, 1.56] with p(d) = 0.05 for this increase in the VA-group. In Fig. 2, the boxplots for the thermo coherence of both groups for T0 and T1 are shown. While at T0 the thermo coherence of both groups was comparable, at T1 the thermo coherence of the VA-group versus control increased significantly ($\chi^2 = 12.32$, df = 7, p-value = 0.09 and d[95%CI] = 0.90 [0.38, 1.42] with p(d) < 0.01).

In Fig. 3, all 10 questions of the ICS-questionnaire, the mean values and standard deviations of all answer scores as well as the Cohens´ d and the p-values are listed. In Fig. 3 concerning the lower diagrams, the profiles of answer scores for both groups are shown for the mean values at T0 and T1. At T0, the mean values for all scores and sub-scores were similar - no significant differences were obtained between both groups (data not shown). At T0, the only noteworthy difference between VA versus control concerned the score for question 7 (Q7): "I came up with good ways to solve problems". In relation to the control-group the VA-group answered this question with an increased score $Q7_C = 3.59 \pm 1.07$ versus $Q7_{VA} = 4.00 \pm 0.71$. The calculation of Pearson´s chi-square χ^2 and Cohens´ d revealed no significant but small effect for the VA-group (d [95%CI] = 0.42 [-0.07, 0.90] with p (d) = 0.09). At T1 significant differences were observed for VA-group versus control (Fig. 3). While the thermo coherence in the VA-group raised considerably (Fig. 2), at T1 also the total-ICS of VA versus control was elevated significantly (table in Fig. 3). Further comparison of the answer profiles at T1 revealed that the scores of questions 1, 2, 3, 4, 8, and 9 were strikingly increased in the VA-group related to the control-group. The calculations of Cohens´ d are listed in the table of Fig. 3. For question 2 (I felt cold without reason) and question 8 (consistency with inner wishes) significant Cohens´ d effects were obtained ($d_{Q2} = 0.53$ with p(d) = 0.04; $d_{Q8} = 0.56$ with p(d) = 0.03).

3.3. Thermo coherence and warmth

45 patients (32 controls and 13 VA-patients) of which completed ICS-questionnaires for T2 were available and surveyed were eligible for the subgroup analysis (Fig. 1). 16 patients (14 control- and 2 VA-patients) not eligible for subgroup analysis were still under follow-up at cut-off time, while 8 controls and one VA-patient dropped out for the 12 months surveillance. For this subgroup, equivalent profiles as for the entire study group (Figs. 2 and 3) were observed for T0 and T1 (data not shown). From boxplots in Fig. 4A it appears that for the VA-group at T2 in relation to T0 the thermo coherence still was significantly increased ($\chi^2 = 9.33$, df = 6, p = 0.16 and d [95%CI] = 1.47 [0.44, 2.50] with p (d) = 0.01).

The individual subjective feeling of warmth during the course of

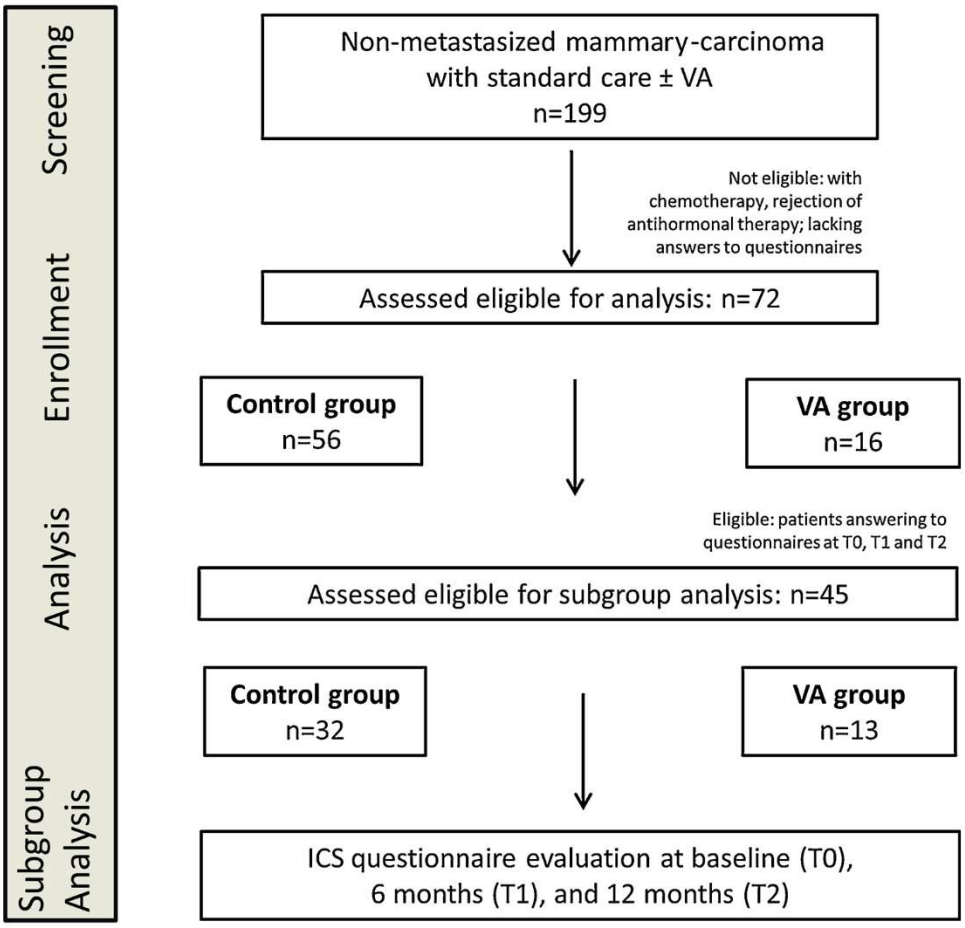

Fig. 1. Flow chart of the study population. Control-group: breast cancer patients treated with guideline-orientated oncological standard therapy; VA-group: patients treated with a combination of guideline-orientated oncological standard therapy and add-on VA-extracts.

time was measured as outlined in the methods and legends to Fig. 4. We observed (Fig. 4B) that at T2 the majority (69%) of breast cancer patients with add-on VA treatment felt an advancement of pleasant warmth, while only 25% of the control group had this feeling. This significant effect ($\chi^2 = 7.941$; df = 2, p = 0.019) remained after adjustment for demographic variables in a multivariable regression analysis (Table 4). Six variables including age, BMI, UICC-stage, hormonal stage, HER2 status, and concomitant VA therapy were adjusted. Age, UICC-stage, hormonal stage, and HER2 status showed no effects while concomitant VA-therapy was associated with a significant increase (estimate β = 0.759 with p = 0.006) of the feeling of pleasant warmth. Furthermore, an obese BMI was positively associated with the

Table 1
Baseline characteristics of primary breast cancer patients.

	Total, n (%)	Control, n (%)	VA, n (%)	*p*-value
Number of patients, n (%)	72 (100)	56 (100)	16 (100)	
Age, years, median (IQR)	62.1 (52.3-70.6)	62.1 (52.3-70.6)	61.5 (52.3-69.7)	p = 0.982
BMI, median (IQR)	24.6 (22.2-27.0)	25.0 (22.2-28.0)	24.0 (22.0-25.0)	p = 0.107
normal (BMI < 25)	40 (55.6)	29 (53.1)	11 (68.8)	$\chi^2 = 2.957$
overweight (25 < BMI < 30)	24 (33.3)	19 (33.9)	5 (31.3)	df = 2
obese (BMI > 30)	8 (11.1)	8 (14.3)	0 (0)	p = 0.228
UICC stages, n (%)				
O	7 (9.7)	6 (10.7)	1 (6.3)	$\chi^2 = 8.305$
I	41 (56.9)	31 (55.4)	10 (62.5)	df = 3
II	22 (30.6)	19 (51.4)	3 (18.8)	p = 0.040*
III	2 (2.8)	0 (0)	2 (12.5)	
ICD-10				$\chi^2 = 0.0$
C50.9 (breast cancer), n (%)	67 (93.1)	52 (92.9)	15 (93.8)	df = 1
D05.1 (DCIS), n (%)	5 (6.9)	4 (7.1)	1 (6.3)	p = 1.0
Hormonal status, n (%)				
Premenopausal	16 (22.2)	12 (21.4)	4 (25.0)	$\chi^2 = 1.236$
Perimenopausal	4 (6.6)	4 (7.1)	0 (0)	df = 2
Postmenopausal	52 (72.2)	40 (71.4)	12 (75.0)	p = 0.539
Estrogen receptor positive	72 (100)	56 (100)	16 (100)	p = 1.0
Progesteron receptor positive	67 (93.1)	55 (98.2)	12 (75.0)	p = 0.008*
HER2 positive	3 (4.2)	2 (3.6)	1 (6.3)	p = 1.0

Table 2
Interventions.

	Total, n (%)	Control, n (%)	VA, n (%)
Surgical interventions, n (%)	69 (95.8)	54 (96.4)	15 (93.8)
Radiation, n (%)	65 (90.3)	52 (92.9)	13 (81.3)
Antihormonal therapy, n (%)	72 (100)	56 (100)	16 (100)
Tamoxifen	49 (68.1)	37 (66.1)	12 (75.0)
Anastrozol	11 (15.3)	10 (17.9)	1 (6.3)
Letrozol	8 (11.1)	6 (10.7)	2 (12.5)
Exemestan	4 (5.6)	3 (5.4)	1 (6.3)
Mistletoe therapy, n (%)	16 (22.2)	0 (0)	16 (100)

Table 3
Number of patients receiving mistletoe therapy.

	Patients, n
Total number of VA patients, n	16
Preparations, n	
Abnobaviscum	8
Iscador	6
Helixor	4
Iscucin	2

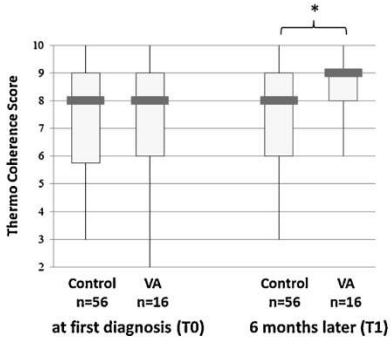

Fig. 2. Thermo coherence at first diagnosis (T0) and after 6 months (T1). For the entire study group (n = 72) the ICS-questionnaires of T0 and T1 were analyzed. The boxplots of thermo coherence scores at T0 and T1 for the control- and VA-group are shown. *Cohens´ d calculation: *d* [95%CI] = 0.90 [0.38, 1.42]; p(d) < 0.01.

feeling of pleasant warmth (Table 4; β = 0.975 with p = 0.019) during anti-hormonal treatment.

4. Discussion

The present study assessed the sense of coherence of 72 primary non-metastasized breast cancer patients treated with endocrine therapy. Six months after first diagnosis an improved sense of coherence for the breast cancer patients, who were additionally treated with VA-applications were observed. In a subgroup of 45 breast cancer patients, a significant association of concomitant VA therapy with a supportive effect on the thermo coherence appeared to persist for 12 months.

Using a set of questionnaires including the ICS, it was previously shown, that in cancer patients under chemotherapy and concomitant VA-therapy substantial differences could be detected [20]. In the present study the influence of add-on VA treatments on breast cancer patients under anti-hormonal therapy without chemotherapy has been evaluated. It is well-established that the sense of coherence has an impact on the HRQL [17]. During cancer treatment a comfort of well-being is often associated with good thermoregulation [25,26], being a precondition on the subject of internal coherence. However, an improvement of thermo coherence as observed for patients additionally treated with VA may contribute to an enhancement of their HRQL.

Utilizing the EORTC QLQ-C30 questionnaire Eisenbraun et al. [9] reported that concurrent treatment of breast cancer patients with VA-extracts and chemotherapy improved and stabilized their HRQL, especially their fatigue-levels were alleviated [33]. In line with these findings, using the EORTC QLQ-C30 questionnaire, we observed a clinical effective improvement (+11.0 with $p < 0.01$) of the global health status in breast cancer patients being treated with a combination of chemotherapy and VA [34]. In the present study we focused on the ICS-questionnaire which addresses the dimension of sense of coherence including thermoregulation in breast cancer patients. The ranges of all detected ICS-total and sub-scores were in line with our previous report [20]. Due to the individual varying form of VA-application, yet no application-dependent conclusions concerning the impact of VA-extracts are possible. In future prospective studies the efficacy of specified VA-applications should be evaluated.

Thermoregulation is regulated between vasoconstriction and sweating, depending on a circadian variation [35] and is associated with the energy balance of the body depending itself on several variables especially body weight, respectively the BMI [36]. In accordance with this we observed a positive association between BMI and all thermo scales of the ICS, for all time points measured and a pronounced improvement of the feeling of warmth for obese patients. Furthermore, from our analyses it can be suspected that the hormonal status play a role for the effects of additional VA-therapy on thermoregulation. A thermal dysregulation (cold acres) has been discussed as a constitutional pattern particularly in premenopausal breast cancer patients [37]. 7 of the control patients and 4 of the VA-patients were premenopausal. All premenopausal VA-patients harmonized their feeling of warmth, while only 3 of the control premenopausal patients felt an increase, and another 3 patients felt a decrease in feeling pleasantly warm during anti-hormonal therapy at 12 months surveillance. A thermal dysregulation such as `feeling cold´ or the feeling of hot flushes and congestive sweating is often seen in patients with breast cancer and can explicitly affect the HRQL [25]. Sudden onset of treatment-induced menopausal symptoms including hot flushes and night sweats are common problems for breast cancer survivors [38]. Pre- and perimenopausal patients could be especially affected [23]. Moreover, it was shown by Moon et al. [39] that menopausal severe symptoms as hot flushes and night sweat in breast cancer survivors can mainly be attributed to tamoxifen. Although to date these symptoms have primarily been reported anecdotally, hot flushes, for instance, have been postulated to be an independent predictor of anti-hormonal therapy [28] while chemotherapy has been linked to 'feeling cold' [25]. Because of the prominence of these symptoms following anti-hormonal treatments it is important to develop alleviation treatments to promote long-term use of endocrine therapy to optimize disease prognosis. Various supplemental treatments, as selective serotonin re-uptake inhibitors, are being investigated, to alleviate menopausal symptoms in breast cancer patients [25]. Breast cancer patients frequently have the desire to treat occurring side effects with alternative and complementary remedies. Some herbal products seem to be effective for menopausal symptoms but unfortunately, only little clinical trials and safety data are available to allow conclusive recommendations [40]. Frequently feeling excessively hot and/or cold under ambient temperature conditions or reports of breast cancer patients feeling inappropriately and persistently cold can be found only as anecdotal information on various breast cancer websites, but to date, has not been scientifically investigated [25]. Breast cancer patients are frequently deficient in achieving thermal comfort. This phenomenon usually is accompanied by further endogenous stress factors which in turn have consequences for the immune system [25]. It is suggested that changes in the level of inflammatory cytokines are responsible for thermal discomfort and also fatigue [25]. The relationship between mistletoe, stimulation of immune functions, and thermoregulation including the induction of fever has been debated in several review articles [41–43]. Our results points to an improvement of the subjective thermo coherence which could be

n=72 T1	Control		VA			
	Mean	SD	Mean	SD	Cohens´d [95%CI]	p-value(d)
Total-ICS Score (Q1-Q10)	37.71	6.38	40.00	5.10	0.75 [0.25, 1.26]	< 0.01*
Subscores:						
Inner Resilience and Coherence (Q1+Q4 to Q10)	30.13	5.10	31.69	4.37	0.38 [-0.11, 0.86]	0.12
Thermo Coherence (Q2+Q3)	7.59	1.94	8.31	1.26	0.90 [0.38, 1.42]	< 0.01*
Questions:						
1) There were times last week, I felt good.	3.73	0.79	4.06	0.66	0.37 [-0.11, 0.85]	0.13
2) I felt cold without reason	3.80	1.22	4.19	0.73	0.53 [0.04, 1.01]	0.04*
3) I felt pleasantly warm	3.79	0.96	4.13	0.70	0.40 [-0.08, 0.88]	0.10
4) I felt my health was:	3.59	0.82	3.94	0.66	0.39 [-0.09, 0.87]	0.11
5) I was able to face the day with confidence	3.89	0.70	4.06	0.75	< 0.3	
6) I felt to have courage to solve problems	4.20	0.85	4.06	0.83	< 0.3	
7) I came up with good ways to solve problems	3.82	0.95	3.88	0.70	< 0.3	
8) what I did every day was consistent with my inner wishes	3.39	0.94	3.81	0.53	0.56 [0.07, 1.05]	0.03*
9) deep down I felt secure	3.68	0.73	3.94	0.66	0.39 [-0.09, 0.87]	0.11
10) I felt moving in the right direction	3.82	0.87	3.94	0.83	< 0.3	

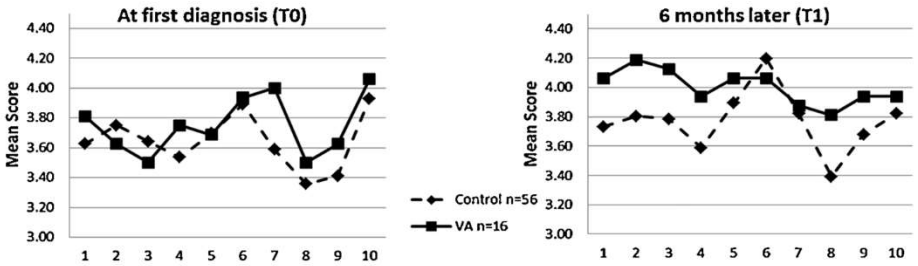

Fig. 3. ICS questionnaire of breast cancer patients. The 10 questions of the ICS questionnaire with answer possibilities 1–5 (1 = low ICS, 5 = high ICS) were determined for T0 and T1. (An English version of the ICS-questionnaire can be found in the Supplementary Appendix.) Mean values and standard deviations of total, subscales, single scores, and Cohens´ d, were calculated and all values for T1 are listed in the upper table. Cohens´ d [95%CI] analyzes and p-values (d) between VA and control groups at T1 were determined using R-statistics. *Significant p(d) < 0.05. In the lower diagrams the profiles of answer score of all 10 questions for both groups are shown for the values at T0 (left) and T1 (right).

related to an improvement of thermoregulation under mistletoe treatment.

Due to the low case numbers in the VA-group in this study, present analysis is limited to first observations on the impact of concomitant VA-treatment in breast cancer patients treated with anti-hormonal therapy. Unwanted biases may have been introduced in the analysis, e.g. the assignment of treatment with add-on VA was performed in a non-randomized, non-controlled and un-blinded fashion and physicians could have unintentionally selected patients with better responsiveness for VA-therapy. Furthermore, other confounders may influence the sense of coherence, especially patients choosing the options to receive VA may differ, and because of the observational nature and low sample size our findings and conclusions have to be handled with caution. Nonetheless, our data are among the first findings on thermo-perception in breast cancer patients under VA and anti-hormonal therapy. Controlled prospective studies with higher case numbers are needed to analyze the influence of VA-therapy in the context of thermoregulation and its impact on HRQL.

Table 4
Influence on the inner feeling of warmth.

n = 45 Feeling of Warmth	estimate	SE	p-value
Demographic Variables			
Age	−0.014	0.016	0.403
BMI			
normal (BMI < 25)	reference		
overweight (25 < BMI < 30)	0.257	0.248	0.308
obese (BMI > 30)	0.975	0.398	0.019*
UICC stage 0	reference		
UICC stage I	−0.037	0.406	0.927
UICC stage II	−0.050	0.456	0.913
UICC stage III	−0.963	0.654	0.149
Hormonal status			
Premenopausal	reference		
Postmenopausal	−0.077	0.206	0.712
HER2 negativ	reference		
HER2 positiv	−0.198	0.462	0.672
Therapy			
control	reference		
VA	**0.759**	**0.260**	**0.006***

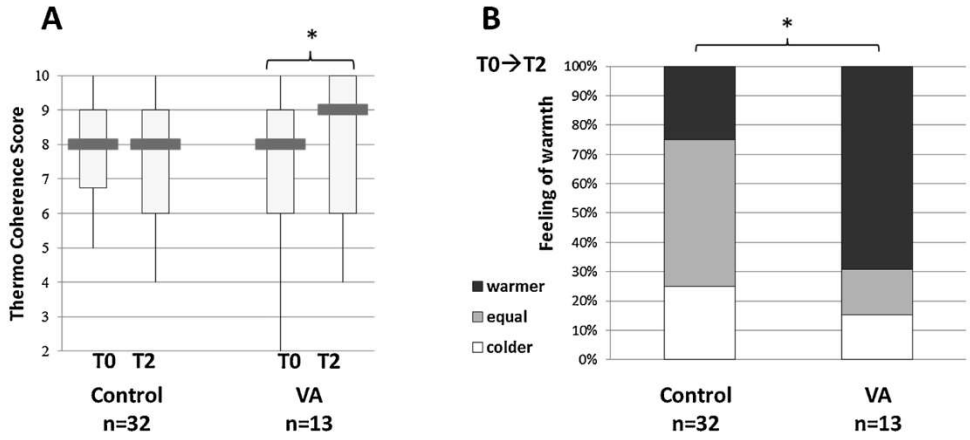

Fig. 4. Thermo coherence and feeling of warmth after 12 months. For the subgroup (n = 45) also the ICS-questionnaires 12 months after first diagnosis (T2) were analyzed. **A**, The boxplots for the thermo coherence scores for the control- and VA-group at T0 and T2 are shown. *Calculation of Cohens´ d revealed for the VA-group *d* [95%CI] = 1.47 [0.44, 2.50] with p(d) = 0.01. **B,** Feeling of inner warmth compared to first diagnosis. The answer scores of the ICS-question 3 "I felt pleasantly warm" were compared between T0 and T2. *warmer*: increase of score; *equal*: unchanged; *colder*: decrease of score.*Chi-square analysis revealed for the VA-group: $\chi^2 = 7.941$; df = 2, p = 0.019.

5. Conclusion

Our findings suggest that VA additionally applied to anti-hormonal therapy improves the sense of coherence and could be a suitable treatment to alleviate thermal discomfort symptoms in early stage breast cancer, especially for premenopausal patients. The available data were of observational nature. Further prospective studies should focus on the effect of integrative treatment regimens including standard therapy and VA on thermoregulation and HRQL in more detail and over longer time periods.

Authors

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Conflict of interest

Friedemann Schad reports grants from Helixor Heilmittel GmbH, grants from Abnoba GmbH, grants from Iscador AG, outside the submitted work. Grants from Helixor Heilmittel GmbH include travel costs and honoraria for speaking. Matthias Kröz received honoraria for lectures from Helixor Heilmittel GmbH outside the submitted work. All other authors declare that no competing financial interests exist.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eujim.2019.03.007.

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