Impact of Complementary Treatment of Breast Cancer Patients with Standardized Mistletoe Extract during Aftercare: A Controlled Multicenter Comparative Epidemiological Cohort Study

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Abstract. *Objectives: To investigate the safety and efficacy of complementary treatment of breast cancer patients with the standardized mistletoe extract (sME) HELIXOR® in routine practice during aftercare through a multicenter comparative epidemiological cohort study with 53 randomly selected hospitals/practices representatively distributed in Germany, including oncologists, gynaecologists and general practitioners. Patients and Methods: Data from 741 screened patients fulfilling the inclusion/exclusion criteria were checked. Of these, 681 patients were eligible for the final analysis of the study group (with sME n=167) and the control group (n=514). Efficacy (development of disease/therapy-induced signs and symptoms; quality of life) and safety (number and severity of adverse events) of complementary treatment in breast cancer patients treated with sME in the aftercare period were determined. Results: Complementary treatment of breast cancer patients with sME during the aftercare period of approximately 5 years after terminating recommended standard therapies resulted in significantly fewer ($p<0.001$) complaints of patients (56.3% study group versus 70.0% control group). The reduced number of disease/therapy-related sign/symptoms (e.g. mucositis, fatigue, pain, headache) correlated to a significantly improved quality of life. Adverse drug reactions to the sME treatment were mostly mild and self limiting. Conclusion: Complementary treatment with the sME HELIXOR® proved to be beneficial for breast cancer patients since it significantly improved quality of life and significantly reduced persistant signs/symptoms of the disease/treatment during the validated aftercare period of approximately five years.*

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Breast cancer is the most frequent female malignancy in the Western world with steadily increasing incidence and mortality during the past two decades (1). It generally requires multimodal treatment consisting of surgery, chemo-, radio- and hormone therapy (1-4). It is mainly during adjuvant chemo-, radio-, hormone-therapy and thereafter that women request complementary treatments to improve quality of life by reduction of side effects and to optimize the success of the tumor destructive standard treatment. While complementary treatments are not an alternative to the evidence-based antineoplastic approaches, they may be valuable in optimizing these therapies (5, 6).

Standardized mistletoe extracts (sME) have been applied to cancer patients for several decades as complementary medications (7-9). They were introduced into oncological treatment by Rudolf Steiner around 1920 and there are many reports on their clinical efficacy (8, 9). However, the evidence of these results is still controversial but with growing acceptance since the problem of adequate methodology in evaluating safety and efficacy of complementary medicine was recently solved (5, 6, 9).

Mistletoe extracts with defined amounts of mistletoe lectin I (ML-I) yielded promising experimental and clinical results (10-12). Recent research showed that the same can be found with standardized mistletoe extracts with a predominant content of ML-III (13). Clinical studies of the evidence-based medicine/EBM-level I (randomized controlled trials) and level II (epidemiological cohort studies) have shown that complementary application of standardized mistletoe extract can significantly reduce the side-effects of standard tumor destructive chemo-

/radiotherapies (13-15). However, EBM-relevant studies of adequate methodology to further evaluate the clinical benefit of standardized mistletoe extracts (especially in the aftercare period) are rare but urgently needed.

Here we report on the assessment of safety and efficacy of complementary application of sME in breast cancer patients during the aftercare period using current methodology for epidemiological cohort studies (representing level II in EBM).

Patients and Methods

Study design. A multicenter comparative epidemiological cohort study in patients suffering from breast cancer was made. The design and conduct of the study were performed in accordance with current standards for epidemiological (observational) cohort studies. Extensive descriptions on design and validity of this type of study is published elsewhere (16-18).

Data were obtained from 53 study centers (hospitals; general/specialized practitioners) in Germany. They were chosen at random from a comprehensive public address database. From the randomly chosen study centers, the case reports of all patients (n=761 patients) treated for primary breast cancer during January 1990 until December 2000 were checked for inclusion/exclusion criteria. Twenty patients had to be excluded from the study since they presented violations of the inclusion/exclusion criteria or incomplete data for the aftercare period (14 patients) and 6 patients had no data for aftercare treatment. This procedure assures representativity of the selected patients within the study centres. During the observation period (study group: mean 4.35 years; control group: mean 3.0 years), 167 patients of the cohort were complementarily treated with standardized mistletoe extract (sME; HELIXOR M, A or P, Helixor Heilmittel GmbH&Co.KG, Rosenfeld, Germany) during the aftercare period, 514 patients did not receive any mistletoe treatment during the aftercare period and 60 patients changed the treatment modalities from study to control group and were excluded from analysis. The inclusion criteria for the study cohort comprised: primary, non-metastasized breast cancer UICC levels I-III; age: 20-80 years; treatment with standardized mistletoe extract HELIXOR® according to the Summary of Product Characteristics within every year of documented follow up (study group) in addition to standard tumor-destructive treatment (surgery: RO-resection; chemo-, radio-, hormone therapy) following international recommendations. Patients were excluded if they received other mistletoe products except the study medication, if they suffered from a relapse or metastatic disease at the beginning of the postoperative treatment, or if a secondary malignancy was detected.

Data collection. Prior to data collection the data elements required for the study were identified and defined in the trial protocol and case report forms (CRFs). Data were acquired by the investigators from the patients' medical records at the study centers and transferred into standardized CRFs. Data collected included patients demographic details, characteristics of the cancer disease and treatment, disease-related symptoms and adverse effects experienced by the patients and the course of the disease. Investigations were regularly performed (at yearly intervals) during the whole observation period. A clinical quality assurance audit was carried out by an independent institution which confirmed that the data were acceptable for the purpose of a clinical trial.

Assignment to treatment and statistical analysis. It was estimated that a sample size of 500 patients was required in the selected cohort with probability 95% of at least one case with seldom events (probability 0.6% in the population). The per protocol sample (patients who met all inclusion criteria and were treated during all aftercare years either with sME (study group) or without sME (control group)) was used for analyses (n=681). For the primary efficacy criterion (quality of life of the patients in the aftercare period depending on persisting adverse effects of treatment or symptoms related to cancer, such as gastrointestinaltract disorders, pain, fatigue, depression) the unadjusted normalization rates (rates of patients without complaints during the aftercare period) were compared between treatment groups with the Chi-square test. Logistic regression analysis was used for detection and elimination of the influence of other treatments and baseline characteristics on the rate of complaints during aftercare, and the odds ratios for complaints between study and control group were adjusted for these covariates. Statistical analysis was performed with SPSS+ for Windows, version 4.0 (SPSS Inc., Chicago IL, USA).

Outcome analysis. Typical disease or therapy-induced symptoms were assessed based on the data collected from the patients' records at the beginning and regularly (at least yearly evaluation) until the end of the observation/treatment period. Symptoms were allocated to scores of 0 (no symptoms) and 1 (symptoms). The following symptoms were recorded: gastrointestinal tract symptoms (nausea, vomiting, change in appetite, stomach pain and stomach disorder), mental conditions (tiredness, depression, memory or concentration disorders, sleep disturbances), headache, tumor pain, cachexia. The primary target criterion was the lack of symptoms during the aftercare period.

Safety. Analysis of safety of the treatment with the sME consisted of the analysis of the number, severity and causality of adverse events, their treatment and outcome.

Results

Characteristics of patients and treatment. Data from the medical records of 761 patients with primary breast cancer were obtained from 53 representative centers (hospitals; general/specialized practitioners) in Germany. The patients were complementarily treated with sME HELIXOR® in addition to recommended standard therapy (study group) or did not receive complementary sME (control group). The primary aim of the study was to evaluate the impact of complementary treatment with sME on typical signs and symptoms in the post surgery, chemo-/radiotherapy, aftercare period. The data from 80 patients were excluded from this analysis because they did not meet the inclusion/exclusion criteria: no data available for the aftercare period: n=6; change of treatment modalities from study group to control group: n=60; other violation of inclusion/exclusion criteria n=14).The final analysis was performed on the data of 681 patients (treated per protocol), of whom 167 were complementarily treated with sME (study group) and 514 without sME (control group).

Table I. *Selected demographic data of the breast cancer patients investigated.*

	Study group			Control group		
	Mean	SD	n	Mean	SD	n
Age (years)	55.11	9.61	167	54.63	10.16	513
Height [cm]	167.75	6.67	160	163.42	6.71	473
Body weight [kg]	70.69	9.50	164	71.62	13.92	473

Table II. *Therapies of the breast cancer patients in the aftercare period.*

	Study group		Control group	
	n	%	n	%
Radiotherapy				
No	162	97.0	500	97.3
Yes	5	3.0	14	2.7
Chemotherapy				
No	163	97.6	500	97.3
Yes	4	2.4	14	2.7
Hormone therapy				
No	47	28.1	266	51.8
Yes	120	71.9	248	48.2

Both groups were comparable in age ($p=0.590$) (Table I), however, with a statistically significant ($p<0.001$) tendency to more severe diseases with higher UICC stages in the study group. The mean duration of follow-up during aftercare was 4.5 years (study group) and 3.0 years (control group). The kind and frequency of adjuvant treatments (chemo-/radio-/hormone therapy) after operation were comparable. During the study-relevant aftercare period, frequency of chemo-/radiotherapy was comparable, however, hormone therapy was significantly more frequent ($p<0.001$) in the study group as compared to the control group (Table II).

Safety of the sME treatment. Amongst the sME-treated cohort the rate of sME associated adverse disease-related symptoms (ADRs) was 10% (n=17). Most ADRs were mild to moderate (n=15) and comprised local reactions, erythema, pruritus, flu-like symptoms. Most ADRs were self-limiting without necessary therapeutic intervention, however, sME administration was stopped because of a generalized reaction in one patient. Since the tolerability of complementary sME treatment was declared good by 94% of the patients in the study group and since the rate and severity of ADRs were low, the treatment with the sME HELIXOR® can be regarded as safe.

Efficacy of the sME treatment in the aftercare of breast cancer patients. The primary aim of this study was to determine whether complementary treatment of breast cancer patients with sME during the aftercare period (after termination of the recommended standard treatment modalities: surgery, chemo-/radiotherapy) could reduce disease/therapy-related signs and symptoms or prolonged adverse effects of the antineoplastic therapies. The primary target criterion was the lack of symptoms during the aftercare period. In the aftercare period, 56.3% of the patients in the study group and 70.0% of the patients in the control group suffered from disease or therapy-related symptoms. The rate of complaints was significantly lower ($p<0.001$) in the patients of the study group as compared to those of the control group. The rates of complaints in the years of aftercare are shown for both groups in Figure 1. In each year evaluated the complaints were less frequent in the study group than in the control group. Except for year 1 the differences are statistically significant.

For unbiased results, the changes in symptom scores were adjusted for the value of the propensity score. To reveal the influence of baseline data and treatments in aftercare on the complaints rate and to get an estimate of the odds ratio of complaints in aftercare between study and control group which is adjusted to similar conditions in both groups, a logistic regression was performed with relevant covariates: age; patients residence; UICC-stage; hormone receptor status; additional diseases; chemo-/radio-/hormone therapies; other therapies during aftercare. The odds ratio of complaints between study and control groups, adjusted for these covariates is 0.508 with a 95% confidence interval from 0.319 to 0.811. The complaints odds of the patients treated with sME HELIXOR® are in the mean half of the complaints odds of patients without this complementary treatment. Table III shows for each symptom investigated and for study and control group the type and overall frequency of complaints during the aftercare period. Whereas gastrointestinal (GI)-tract disorders (nausea, vomiting, diarrhea) were obviously more frequent in the study group, mental disorders (fatigue, pain, headache) and mucositis were more pronounced in the control group. Concerning the rates of re-operation, relapse and metastasis, complementary sME administration did not show a significant benefit for breast cancer patients during the limited observation period (Table IV).

Four (2.4%) patients of the study group and 9 (1.8%) of the control group died during aftercare.

Discussion

Epidemiological methods in collecting and analyzing existing clinical data provide a means not only to evaluate safety and efficacy of a particular treatment, but also to generate hypotheses for the development of well-designed

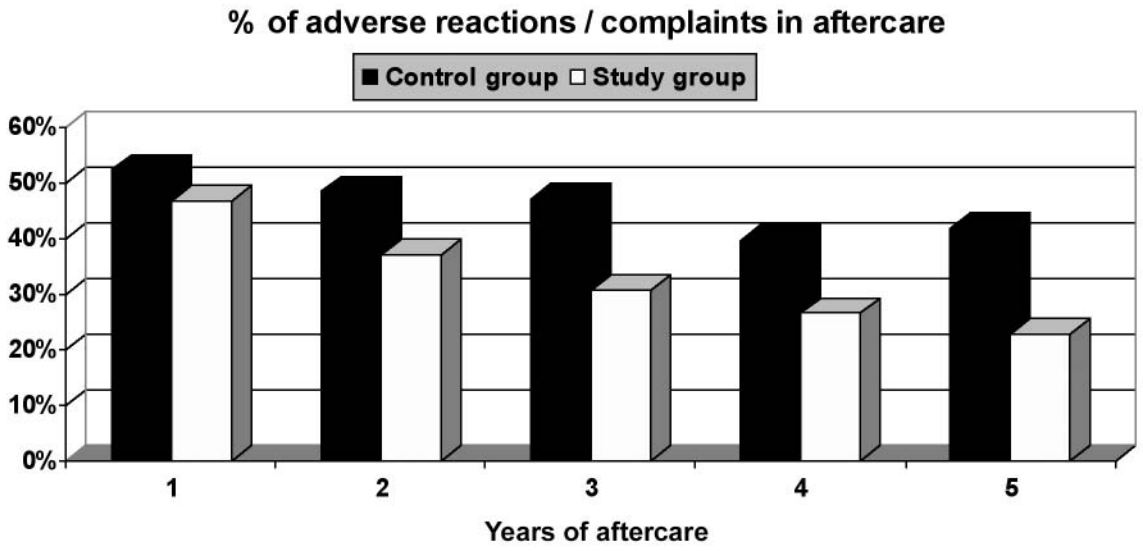

Figure 1. *Overall adverse reactions/complaints of breast cancer patients in the aftercare period with complementary treatment with sME HELIXOR® (study group) or without (control group).*

Table III. *Specification of the complaints during the aftercare period of the breast cancer patients investigated.*

	Study group		Control group	
	n	%	n	%
Vomiting/GI-tract disturbance				
No	152	91.0	482	93.8
Yes	15	9.0	32	6.2
Tumor pain				
No	130	77.8	309	60.1
Yes	37	22.2	205	39.9
Head achea				
No	166	99.4	502	97.7
Yes	1	0.6	12	2.3
Tiredness/fatigue				
No	166	99.4	509	99.0
Yes	1	0.6	5	1.0
Depression				
No	146	87.4	498	96.9
Yes	21	12.6	16	3.1
Sleep disturbances				
No	141	84.4	442	86.0
Yes	26	15.6	72	14.0
Kachexia				
No	109	65.3	350	68.1
Yes	58	34.7	164	31.9
Bleeding				
No	158	94.6	475	92.4
Yes	9	5.4	39	7.6
Mucositis				
No	166	99.4	507	98.6
Yes	1	0.6	7	1.4

Table IV. *Rate of relapse, metastases and operations during the aftercare period in the breast cancer patients investigated.*

	Study group		Control group	
	n	%	n	%
Relapse				
No	161	96.4	499	97.1
Yes	6	3.6	15	2.9
Metastases				
No	161	96.4	492	95.7
Yes	6	3.6	22	4.3
Operations				
No	162	97.0	501	97.5
Yes	5	3.0	13	2.5

controlled clinical studies (18-20). It is the goal of the scientific community to subject all cancer treatments to rigorous evaluation through appropriately designed and conducted clinical trials. This epidemiological cohort study was designed to investigate the impact of complementary treatment with sME HELIXOR® on the quality of life of breast cancer patients during a defined aftercare period of approximately 5 years. The primary aim of this study was the analysis of disease or therapy-related symptoms (complaints) in parallel groups of patients complementarily treated with sME (study group) or without it (control group). Further questions to be addressed were the safety of the sME treatment and the evaluation of the associated quality of life.

The presented data collected on 681 per protocol treated breast cancer patients included a wide range of standard and complementary treatment schemes, however, rigorous exclusion/inclusion criteria were strictly observed and provided an evaluable cohort. The analysis of a large body

of data by epidemiological cohort studies is a sensitive and valid approach for achieving this goal. It was shown recently that the results of well-designed epidemiological cohort studies do not indicate consistently greater magnitudes of treatment effects and are not qualitatively different from those of randomized controlled trials (20). Studies such as these can be used to demonstrate the safety and efficacy of empirically administered medications and to generate hypotheses for randomized controlled trials.

For this study, only breast cancer patients who did receive conventional aftercare therapies without (control group) or with the addition of sME (study group) were selected and evaluated. The results show that complementary sME treatment of breast cancer patients during an aftercare period of approximately 5 years was statistically superior to the control group in reducing persistant disease or therapy-related symptoms, such as fatigue, pain and headache. The results suggest that the administration of sME stabilized and improved the quality of life of the breast cancer patients by its impact on disease or therapy-related symptoms. As the tolerability of complementary sME treatment was good and only a low rate of mostly mild to moderate adverse reactions was recorded, the treatment with sME can be regarded as being safe. In the case of persistant symptoms of the causative diseases or adverse effects of standard tumor-destructive therapies in breast cancer patients, complementary treatment is a beneficial option to reduce these complaints and to improve the quality of life. The data presented suggest that complementary administration of the sME HELIXOR® might be beneficial for breast cancer patients during the aftercare period.

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