Reprint Antibiotika · Chemotherapeutika · Virustatika · Zytostatika

ArzneimForschDrugRes

Antibiotics · Antiviral Drugs · Chemotherapeutics · Cytostatics

Efficacy and Safety of Long-term Complementary Treatment with Standardised European Mistletoe Extract *(Viscum album L.)* in Addition to the Conventional Adjuvant Oncological Therapy in Patients with Primary Non-metastatic Breast Cancer

Results of a multicentre, comparative, epidemiological cohort study in Germany and Switzerland

Paul R. Bock[a], Walter E. Friedel[b], Jürgen Hanisch[a], Marita Karasmann[a], and Berthold Schneider[c]

Institute for Medical Research and Statistics, IFAG Basel AG[a], Basel (Switzerland), Hospital Bad Bocklet, Department of Oncology[b], Bad Bocklet (Germany), and Institute of Medical Statistics, University of Hannover, Medical School[c], Hannover (Germany)

Summary

Objectives: The purpose of the study was to evaluate the therapeutic efficacy and safety of long-term complementary therapy in primary, non-metastatic breast cancer patients in UICC stage I–III with a standardized European mistletoe extract (*Viscum album L.*, Iscador®, "mistletoe extract") given in addition to conventional adjuvant oncological therapy (i.e. chemo-, radio-, and hormonal therapy; "conventional therapy").

Methods: The multicentre, comparative, retrolective, pharmaco-epidemiological cohort study with parallel groups design and randomly selected centers was carried out according to Good Epidemiological Practice (GEP) rules. The study group patients received subcutaneous mistletoe extract injections for at least three months in addition to the conventional therapy, while the control group was treated with conventional therapy only. The patients were followed up for at least three years or until death. The primary endpoint for efficacy was the overall incidence of adverse drug reactions (ADRs) attributed to the conventional therapy. Secondary endpoints were symptoms associated with disease and treatment, as well as the survival. All endpoints were adjusted to baseline imbalance, therapy regimen and other confounders by the logistic regression or the Cox proportional hazard regression. Safety was assessed by the number of patients with ADRs attributed to the mistletoe extract treatment, the ADR severity and the evaluation of a possible tumor enhancement.

Results: 1442 patients (710 study and 732 controls) were eligible for the "per protocol" analysis of efficacy and safety.

Key words

- **Breast cancer**
- **Iscador®**
- **Mistletoe, adjuvant therapy, cohort study, efficacy, safety**
- ***Viscum album L.***

Arzneim.-Forsch./Drug Res. 54, No. 8, 456–466 (2004)

At baseline, the mistletoe extract group had a more advanced disease and worse prognostic factors profile. After a median follow up of 67 vs. 61 months, and a median mistletoe extract therapy duration of 52 months, significantly fewer study group patients (16.3 %) than control patients (54.1 %) developed one or more ADRs attributed to the conventional therapy (adjusted odds ratio (95 % confidence interval, CI): OR = 0.47 (0.32–0.67), p < 0.001). In the mistletoe extract group, several symptoms more frequently disappeared, and the overall estimated survival was significantly longer (adjusted mortality hazard ratio (95 % CI): HR = 0.46 (0.22–0.96), p = 0.038). Systemic ADRs attributed to the mistletoe extract treatment developed 0.8 %, and local ADRs 17.3 % of the patients. The ADR severity was mild to intermediate (WHO/CTC grade 1–2). Severe mistletoe extract therapy-related ADRs or tumor enhancement were not observed.

Conclusions: The results of the present study confirmed the safety of the complementary therapy of patients with primary, non-metastatic breast cancer with a standardized mistletoe extract and showed considerably fewer ADRs attributed to concurrent conventional therapy, as well as reduced disease and treatment-associated symptoms, and suggested a prolonged overall survival in the mistletoe extract group as compared with controls.

1. Introduction

Breast cancer has the highest incidence (25.9 %) and mortality (17.1 %) of all types of cancer in women in Germany. In the United States about 175,000 new cases occur each year and approximately 43,000 women die of breast cancer in the USA and about 1 million women world-wide [1, 2]. Treatment of breast cancer requires multimodal therapy with primary surgery followed by adjuvant radio-, chemo- and/or hormonal therapy depending on individual criteria relating to tumour status, lymph node disease, menopause and hormone receptor status (adjuvant therapy) [3–6]. In view of the frequent side effects of adjuvant therapy [7, 8] and the risk of a substantial impairment in quality of life [9–14], complementary treatment to limit or prevent the symptoms associated with the disease or treatment is becoming increasingly important. This is despite the fact that there is still no convincing evidence of its effectiveness in reducing the progression of the disease and prolonging survival [15–17]. Of the complementary treatments used by cancer patients, European mistletoe extracts *(Viscum album L.)* are the most common in Europe, especially in Germany [18, 19]. In recent studies the most important components of mistletoe (lectins, viscotoxins and other components) have been defined more accurately, their properties researched in pharmacological and toxicological studies and the extract standardised for its active components. In-vitro and in-vivo investigations have identified immunomodulatory and cytostatic effects (overview in [20–23]). However so far only individual case reports and results from smaller, non-randomised studies support prophylaxis of tumour recurrence and extended survival. Controlled clinical studies that have been published show conflicting results and have methodology weaknesses (overview in [24–26]). Discussion of the safety and possible toxicity of mistletoe extracts has also been controversial [27–29]. There are practical and ethical reservations concerning implementation of randomised, controlled trials (RCT) to prove extension of survival, as these trials would have to be carried out over a prolonged period (5 to 10 years) and in view of the relatively good prognosis for non-metastatic breast cancer they would have to include a large number of patients.

For this reason we decided to carry out a retrolective, controlled, epidemiological cohort study using the IFAG standard concept Retrospect™ [30]. This type of study is recognised in epidemiological research [31, 32] and according to EU guidelines permits valid statements to be made on the efficacy and safety of medicinal products that have been on the market for some time ("well established use") [33]. Controlled, epidemiological studies can also achieve EBM evidence level II and thus contribute to the clinical evidence of efficacy [34, 35]. Detailed literature comparisons of the results of randomised, controlled studies with those of controlled, epidemiological observational studies have shown that well designed, implemented and analysed epidemiological studies generally have similar results to randomised, controlled studies [36–40].

The aim of this study was to investigate under practice conditions the efficacy and safety of standardised European mistletoe extract *(Viscum album L.*, Iscador®[1)], "mistletoe extract") as complementary treatment in addition to conventional therapy in the long-term postoperative care of primary non-metastatic breast cancer. This mistletoe extract has been on the market for a long time and is often used as complementary cancer treatment, especially in Germany and Switzerland.

[1)] Manufacturer: Weleda AG, Arlesheim (Switzerland).

Arzneim.-Forsch./Drug Res. 54, No. 8, 456–466 (2004)

2. Material and methods

2.1. Study design

This is a multicentre, controlled, retrolective cohort study. The study group was made up of patients with non-metastatic breast cancer who were treated after surgery with mistletoe extract in addition to conventional chemo-, radio- or hormonal therapy. The control group included patients who received only conventional therapy.

2.2. Selection of centres

A random sample of hospitals and clinics involved in primary cancer care, oncological postoperative care clinics (Reha clinics) and oncological treatment care centres in Germany and Switzerland was selected, which provide postoperative care of patients with breast cancer and which were willing to participate in the study. In the centres either the mistletoe extract was used as complementary treatment in addition to conventional therapy or conventional treatment only was used. There were no restrictions on the type of conventional treatment or other additional measures such as physiotherapy.

2.3. Selection of patient data

In the centres the medical records were obtained for all those patients treated from 1988 to 2000 as part of postsurgical breast cancer care. Treatment could have been completed at the start of the study or still be ongoing (retrolective concept). Patient data were included in the study chronologically and without any further selection. They had undergone surgery for histologically proven, non-metastatic breast cancer (UICC classification I–III). They had to have received postoperative care together with conventional treatment for at least 6 months (chemo-, radio- and hormonal therapy), with or without additional treatment with mistletoe extract. The follow-up time had to have lasted a minimum of 3 years (or until death) and the following essential data were recorded: a) baseline data (age, menopause, hormone receptor status, tumour staging), b) surgery and tumour characterization (time, type, site, multiplicity, UICC classification, staging, grading), c) details of treatment (conventional treatment, mistletoe extract, adjuvant therapies) and d) follow-up findings (Karnofsky index, treatment- or disease-associated symptoms, tumour status, adverse drug reactions (ADRs) of conventional treatment and mistletoe extract, incidence of recurrence, metastases or death).

2.4. Conduct of the study

Data of patients included in the study were transferred from medical records onto standardised case report forms (CRFs) in an anonymous form by clinical trial investigators after briefing by trained monitors. Information on treatment- or disease-associated symptoms was supplemented by an evaluation of the progress of the disease by the doctor. Data on the CRFs were checked for completeness and plausibility, corrected if necessary, and written information (e.g. medicinal products, diagnoses, ADRs) was converted into standardized codes (e.g. code from the ROTE LISTE®, ICD-10, WHO/CTC etc.) and entered into a database system. Audits were carried out on random samples to confirm that data on the CRF corresponded to that in the medical records.

2.5. Parameters and statistical analysis

The primary target criterion of efficacy was the incidence of ADRs of conventional treatment. The secondary target criteria were the symptoms related to the disease and treatment and survival. Treatment safety was evaluated by the incidence and severity of ADRs due to mistletoe extract treatment and any possible tumour enhancement. Since allocation to the study and control group was not randomised it could be assumed that both groups differed regarding essential baseline and treatment conditions. In the statistical analysis differences were determined for all essential conditions and their influence on the target parameters analysed. Prior to comparison of the study and control group the target criteria were adjusted to the same conditions. The multivariate adjustment for the baseline inhomogeneity, treatment measures and other influential factors (confounders) was carried out using logistic regression (for ADRs and symptoms) or Cox proportional hazard regression (for survival). Analysis was carried out using the per protocol method.

3. Results

3.1. Study centres and patient numbers

Sixteen centres in Germany and Switzerland took part in the study; 9 of the centres were clinics or hospitals, of which 5 were for primary care and 4 were for oncological postoperative care (Reha centres), and there were also 7 oncological treatment care centres. 4 centres used both complementary treatment with the mistletoe extract in addition to conventional treatment and also conventional treatment on its own, 9 centres used only conventional treatment supplemented by complementary treatment with the mistletoe extract and 3 centres used conventional treatment only.

In total, data from 1,442 patients were recorded that met the criteria for inclusion. Of these 710 had received the mistletoe extract in addition to conventional treatment (study group) and 732 had received conventional treatment only (control group).

3.2. Baseline data

Table 1 shows the patient baseline data separated according to treatment groups. There are significant and clinically relevant differences between both groups in the period between diagnosis and surgery (1.32 to 0.14 months), a positive oestrogen receptor status (72 % to 65 %), post-menopausal status (62 % to 82 %) and the incidence of non-oncological diseases (36 % to 54 %). Table 2 gives the findings at surgery. Patients in the study group had considerably poorer prognostic values for tumour staging (pT) and tumour grade (pG) and had a higher incidence of multilocular tumours (25 % to 9 %) than the control group. Postoperatively a residual tumour was present in 3 % of the study group and 0.5 % of the control group. Overall the patients' disease was more severe and risk factors for progression were greater in the study group.

3.3. Primary treatment (conventional treatment)

The median observation period for postoperative care was 66 months in the study group and 60 months in the control group. It was therefore comparable for both

Table 1: Demographic and medical history data.

Demographic and medical history data	Study group n = 710	Control group n = 732
Age (years), mean value	53	57
Weight (kg), mean value	67	72
Months between diagnosis and surgery, mean value	1.32	0.14
Estrogen receptor positive	72.5 %	65.1 %
Post-menopause	61.6 %	82.4 %
History of allergies	12.8 %	7.6 %
Non-oncological diseases	36.0 %	53.9 %

Table 2: Surgery and tumour characterization.

Surgery and tumour characterization	Study group n = 710	Control group n = 732
Tumour staging pT2-4	61.4 %	50.3 %
Lymph node involvement N > 0	46.3 %	40.7 %
Tumour grade pG3-4	36.1 %	18.0 %
Tumour staging II + III (UICC)	73.0 %	62.0 %
Multilocular tumour	25.0 %	8.9 %
Surgery with axillary resection/ clearance	59.3 %	76.0 %
Multiple tumour surgery	7.7 %	1.6 %
Residual tumour post surgery	2.7 %	0.5 %

groups. Table 3 gives an overview of primary oncological treatment. Clinically relevant differences are evident between the study groups. 156 patients (22 %) in the study group and 42 (6 %) in the control group had not received any conventional treatment. Radiotherapy was used in 44 % in the study group and in 76 % in the control group. Chemotherapy was used in 33 % in the study group and in 23 % in the control group, whereas hormonal therapy was given to 50 % of patients in both groups.

The median value for the duration of mistletoe extract treatment was 52 months in the study group and the mean cumulative dose of mistletoe extract was 4.367 mg.

3.4. Reduction in adverse drug reactions (ADRs) of conventional treatment

In 112 patients in the study group (16 % of total, 20 % of patients who underwent conventional treatment) a total of 152 ADRs were recorded for conventional treatment, and in 395 patients in the control group (54 % of total, 57 % of patients who underwent conventional treatment) a total of 780 ADRs was found. The ADR rate for primary treatment was therefore considerably and statistically highly significantly lower in the study group than in the control group (adjusted relative ratio (odds ratio, 95 % confidence interval): OR = 0.47 (0.32–0.67), $p < 0.0001$) (Fig. 1). This effect was similar in patients who received radio-, chemo-, or combination therapy. Of the 152 ADRs of conventional treatment in the study group, 40 (27 %) were attributed to radiotherapy (17 of them skin reactions), 89 (60 %) to chemotherapy (42 had nausea/vomiting and 10 leucopenia/leucoyctosis), 8 (5 %) to hormonal therapy and 12 (8 %) to other treatments. Three ADRs could not be classified. Of the 782 ADRs of conventional treatment in the control group, 541 (69 %) were related to radiotherapy (of these 243 were skin reactions), 184 (24 %) to chemotherapy (of these 71 were nausea/vomiting and 6 were leucopenia/leucoyctosis), 15 (2 %) to hormonal therapy and 40 (5 %) to other treatments. Two ADRs could not be classified.

Table 3: Conventional and adjuvant oncological therapy.

Conventional treatment	Study group n = 710	Control group n = 732
No conventional treatment	22.0 %	5.7 %
Radiotherapy	43.9 %	75.7 %
Chemotherapy	32.8 %	23.2 %
Hormonal treatment	50.1 %	50.3 %
Antiemetics	8.6 %	4.9 %
Analgesics	4.5 %	6.0 %
Others (e.g. vitamins)	24.8 %	7.9 %
Physiotherapy	18.9 %	35.1 %
Months between surgery and start of treatment (mean value)	1.4	1.2

3.5. Reduction in disease-related symptoms in the postoperative care period

Medical records were used to establish which symptoms associated with the disease had occurred since the start of postoperative care and whether these symptoms were still present at the end of postoperative care or whether they had disappeared. The following were judged to be disease-associated symptoms: nausea,

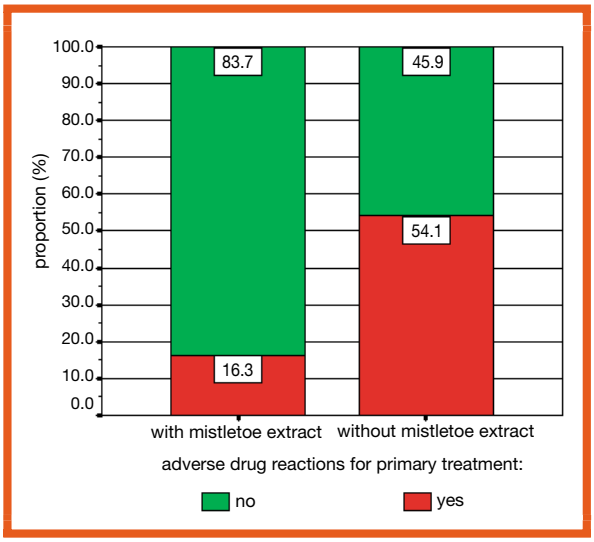

Fig. 1: Proportion of patients with adverse drug reactions (ADRs) after conventional treatment. Adjusted relative ratio (odds ratio): OR = 0.47 (0.32–0.57), p < 0.0001.

Arzneim.-Forsch./Drug Res. 54, No. 8, 456–466 (2004)

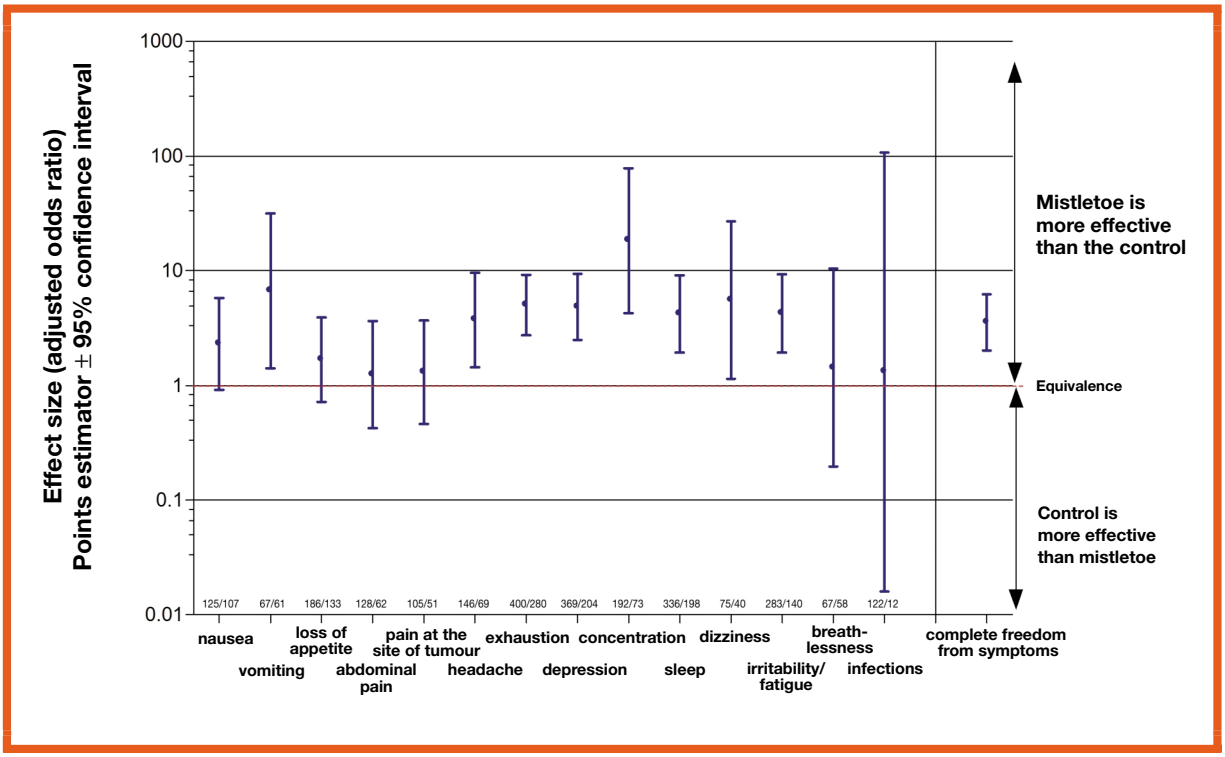

Fig. 2: Incidence of symptoms, adjusted relative ratio (odds ratio) and 95 % confidence interval for complete disappearance ("cure") at the end of the postoperative care period of individual symptoms present initially.

vomiting, loss of appetite, pain at the site of tumour surgery, headaches, tiredness/exhaustion, loss of drive/depression, disturbances in concentration/memory, sleep disturbances, dizziness/disorders of balance, fatigue/irritability, shortness of breath on exertion and infection. For individual symptoms Table 4 gives the numbers (n) of patients in whom the relevant symptoms occurred in the postoperative care period, the number and frequency with which they disappeared (i.e. patients who had no more symptoms at the end of the postoperative phase) and the relative ratios adjusted to the same conditions (odds ratio) between the study and control group, together with their 95 % confidence interval. Fig. 2 gives the confidence intervals for the adjusted odds ratios. The table and figure show that for all the symptoms the estimated value for the relative

Table 4: Incidence of symptoms associated with the disease and freedom from symptoms (explained in the text).

Symptom	Study group			Control group			Adjusted odds ratio "symptom free"	95 % confidence interval
	n	symptom free at the end	%	n	symptom free at the end	%		
Nausea	125	104	83	107	51	48	2.305	0.916–5.800
Vomiting	67	62	93	61	29	48	6.677	1.414–31.525
Loss of appetite	186	139	75	133	58	44	1.679	0.719–3.924
Abdominal/epigastric pain	128	85	66	62	32	52	1.244	0.427–3.624
Local pain at the tumour site (breast)	105	73	70	51	34	67	1.305	0.464–3.666
Headaches	146	99	68	69	15	22	3.734	1.446–9.642
Tiredness/exhaustion	400	275	69	280	88	31	5.020	2.730–9.232
Loss of drive/depression	369	258	70	204	77	38	4.845	2.493–9.418
Disturbances in concentration/ memory	192	111	58	73	19	26	18.355	4.284–78.647
Sleep disturbances	336	154	46	198	87	44	4.210	1.946–9.109
Dizziness/balance disorder	75	44	59	40	13	33	5.557	1.138–27.141
Fatigue/irritability	283	219	77	140	50	36	4.228	1.929–9.268
Shortness of breath on exertion	67	5	7	58	5	9	1.431	0.197–10.417
Infections	122	99	81	12	3	25	1.322	0.016–107.11
Freedom from symptoms at the end of the postoperative care period	558	436	78	569	219	39	3.563	2.026–6.268

ratio is greater than 1. This means that the ratio of patients free of symptoms at the end of the postoperative care period is larger in the study group than in the control group. For many symptoms the lower limit of the confidence interval was greater than 1, which indicates a significantly higher ratio for the study group. Of the 558 patients in the study group who had symptoms in the postoperative period, 436 (78 %) were free of symptoms at the end of the period. Of the 569 patients in the control group with symptoms, 219 (39 %) were free of symptoms. The incidence of symptoms during the postoperative care period was therefore considerably reduced by the supplementary mistletoe extract treatment.

3.6. Survival

97 (13.7 %) of the 710 patients in the study group and 49 (6.7 %) of the 732 in the control group died during the observation period. The higher mortality rate in the study group is largely due to the differences in the baseline situation and conventional treatment between both groups, with the study group being much more seriously ill (see Tables 2 and 3). The non-adjusted mortality rates therefore give a distorted picture and cannot be interpreted directly. To determine the influence of the baseline situation, the risk profile and conventional treatment on mortality and to obtain an unbiased estimate of survival, a Cox regression analysis was undertaken. In this regression it is assumed that the hazard rate (i.e. the time-related probability of dying at a certain time if the person has survived to the time) is composed multiplicatively of a function related only to time, and function unrelated to time for the influencing factors (proportional hazard rate model). In this way it is possible to estimate separately the influence of individual factors unrelated to time ("confounder") on survival (the hazard rate) and the expected survival in the study and control group for the same conditions in both groups (adjusted course). The influence of a factor (relative to the absence of the factor) is quantified by the hazard ratio HR. This gives the value by which the hazard rate is changed if the factor is present, compared to the absence of the factor. For an HR greater than 1 mortality is increased by the factor, if the HR is less than 1 it is reduced. If the HR = 1 the factor has no influence on mortality. The most important influencing factors ("confounders") found in this study (the estimated HR value and the 95 % confidence interval given in brackets) are as follows:

a) Advanced tumour stage (UICC = III: HR = 3.61 (1.61–8.12), p = 0.002; b) use of *prophylactic* conventional treatment (i.e. treatment *before* recurrences or metastases first occur): HR = 0.34 (0.17–0.69), p = 0.003; c) use of concomitant physiotherapy or balneotherapy: HR = 0.41 (0.25–0.69), p = 0.001. If the influence of these and other factors (age, hormone receptor status, menopause, time of surgery after diagnosis, risk profile from tumour stage, grade, multiplicity and residual tumour, concomitant diseases and centre) are adjusted for mortality, an HR of 0.46 with a 95 % confidence interval of 0.22 to 0.96 (p = 0.038) is produced for the influence of the study group compared with the control group on overall mortality. According to the estimated HR, the hazard rate (i.e. the estimated risk of dying) in the study group would only be about half the hazard rate of the control group. Nevertheless the upper confidence interval for HR amounts virtually to 1; i.e. with a 95 % probability, under certain circumstances the "true" hazard rate of the study group can also be only a little lower than that of the control group. Fig. 3 shows the survival curves for the study and control group calculated using the adjusted HR (and the time factor hazard rate calculated from all the data). The survival curve calculated for the study group is always above the curve for the control group, which means a higher estimated probability of survival. For tumour-related death, after ad-

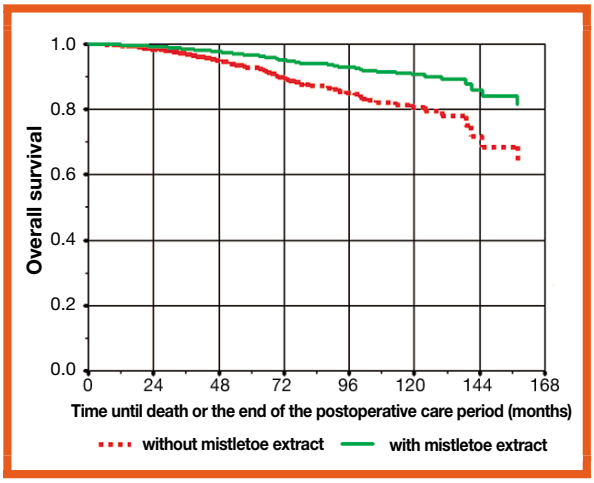

Fig. 3: Overall survival (Cox proportional hazard regression). Adjusted hazard ratio: HR = 0.46 (0.22–0.96), p = 0.038.

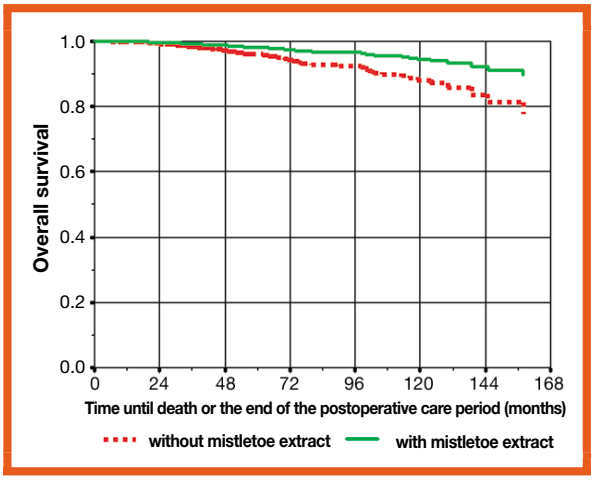

Fig. 4: Tumour-related survival (Cox proportional hazard regression). Adjusted hazard ratio: HR = 0.44 (0.17–1.15), p = 0.093.

Arzneim.-Forsch./Drug Res. 54, No. 8, 456–466 (2004)

justing for inhomogeneity and reference to the same conditions for both groups, an estimated HR value of 0.44 (0.17–1.15) is reached, which is not significantly different from 1 (p = 0.093). However, tumour-related mortality adjusted to the same conditions is lower for the study group than for the control group. As the differences are not significant, it can be concluded at most that there is a trend in favour of the mistletoe extract treatment. The tumour-related survival curves for both groups are shown in Fig. 4. The differences between the treatment groups regarding the incidence of recurrence (recurrence: HR = 0.98 (0.60–1.62), p = 0.947) are not significant.

The adjusted hazard rates for both groups are virtually the same. For the incidence of distant metastases the adjusted hazard rate for metastases-free survival between the treatment groups is not significantly different with HR = 0.65 (0.35–1.21), p = 0.172.

3.7. Safety of mistletoe extract treatment

In 6 of 710 patients from the study group (0.8 %), systemic ADRs were reported that were definitely or probably related to mistletoe extract treatment (weakness, hyperactivity, increase of a topic eczema, tiredness/exhaustion, bacterial skin infection, malaise, gastrointestinal symptoms). The severity was rated as "mild" or "moderate" (WHO/CTC stage 1–2). The ADRs generally lasted for a day. There were no serious systemic ADRs. Local reactions at the injection site (erythema, induration, oedema, itching, pain, sometimes with mild fever reaction) were observed in 123 patients (17.3 %). 71 % of local reactions were mild and had regressed spontaneously. In 7 patients treatment had to be changed, and mistletoe extract treatment was discontinued in 4. There were no indications of any tumour enhancement.

4. Discussion

The results of this retrolective cohort study, in which data from 1,442 patients with primary, non-metastatic breast cancer were recorded in 16 different centres in Germany and Switzerland, show that complementary treatment with standardised mistletoe extract in addition to primary conventional treatment (radio-, chemo-, hormonal therapy) can reduce substantially and significantly the adverse drug reactions of conventional treatment and disease-associated symptoms. The baseline situation and the treatment conditions did, however, differ between the patients treated with and without mistletoe extract and also varied between the centres. These differences also influenced the treatment results, especially survival. When the differences and hazard rates (i.e. the probability of dying at a certain time, if the patient has survived to this time) were adjusted to the same conditions using Cox regression, overall mortality showed a significantly lower hazard rate for the study group with mistletoe extract compared with treatment without the mistletoe extract. However, the difference is no longer significant in the individual subgroups for tumour-related death, recurrence and distant metastases, although there was still a visible trend towards more favourable results in the mistletoe extract group for tumour-associated death and distant metastases. When interpreting these results it must be taken into account that the adjusted hazard rates were not directly observed results but were predicted values based on the reported data calculated under the assumption of the same conditions. The non-adjusted mortality observed varied considerably between the centres over a range of 0 to 33 %. In a subgroup analysis it was only possible to carry out a direct comparison of mortality between the study and control group within the centres in 3 of the postoperative care centres. They had administered treatment with (73) and without (293) mistletoe extract and the baseline situation of the patients and the conventional treatment was comparable. Non-adjusted overall mortality in these centres was 2.7 % (2 of 73) for treatment with the mistletoe extract and 6.5 % without mistletoe extract (19 of 293). The ratio of hazard rates between the study and control group (the adjusted hazard ratio, HR) was 0.38 (95 % confidence interval 0.08–1.74) in these centres and is therefore comparable to the adjusted HR for overall mortality in all centres (HR = 0.46). This can be regarded as an indication that it is quite possible for such a relevant reduction in overall mortality to occur in reality with the mistletoe extract treatment if conditions are appropriate.

In the past, many predominantly empirical results from case studies, case reports and small and non-controlled studies on treatment of malignant tumours with mistletoe extracts have been published. However, critical evaluation of the methods and results often revealed serious weaknesses in methodology [24–26]. In more recent, controlled, randomised studies in head and neck cancer and non-small cell lung cancer (NSCLC) no significant effect of treatment with mistletoe extract on tumour recurrence and survival was found [41, 42]. One of the possible explanations for lack of informative results for these studies could be the suboptimal duration of mistletoe extract treatment of one year or less, whereas with the present cohort study optimal results for survival can only be expected after three or more years. However, there are several controlled, prospective studies in which the clinical efficacy of mistletoe extract therapy on tumour-related results could be confirmed. In a prospective, comparative, clinical study in patients with breast cancer, given either mistletoe extract treatment or combined chemotherapy who were compared with a non-treated breast cancer group, a significantly longer survival time was recorded in the mistletoe extract and combination chemotherapy group [43]. Significantly prolonged survival was also found with mistletoe extract treatment in a randomised "matched-pairs" study, nested in a prospective, non-

randomised study of solid tumours, in particular breast cancer. The patients received conventional treatment, either with or without supplementary mistletoe extract treatment [44]. However this study was criticised for problems in its methodology. In a randomised, clinical study in patients with advanced stage III/IV glioma a significantly longer survival time was found in the mistletoe extract treatment group [45]. The most important reasons for the controversy surrounding the studies named were discussed by Kiene and Edler [24, 26]. In a more recent, multicentre, comparative, retrospective cohort study in patients with primary, non metastatic breast cancer, treated with short-term (median one year) complementary treatment using another standardised mistletoe extract, significantly fewer tumour recurrences were found compared with non-treated control patients but there was no effect on survival. This could be explained by the mistletoe treatment and the postoperative follow-up period being too short [47]. Despite all the weaknesses in the studies quoted there are consistent indications of possible prolongation of survival associated with mistletoe extract treatment, at least for certain types of cancer and treatment regimens. To clarify further the efficacy of mistletoe treatment on the survival of cancer patients, additional studies with optimised treatment design should be carried out.

Regarding the influence of complementary treatment with mistletoe extracts on quality of life criteria and disease- and treatment-associated symptoms of cancer patients, the results published on the frequent significant clinical advantage of complementary mistletoe extract treatment are more convincing and conclusive. The results of the present cohort study confirm a relevant and significant advantage of complementary treatment with standardised mistletoe extract on symptoms and quality of life in patients in the early stages of breast cancer. This is supported by prospective, controlled studies. In the randomised NSCLC study mentioned the general subjective health status in the mistletoe extract group was improved significantly more than in the placebo group [41]. In another prospective, open cohort study in 884 cancer patients, 36 % with breast cancer, most of the quality of life criteria improved considerably within only 3 months of starting treatment with a lectin-1 standardised mistletoe extract [48]. In a prospective, randomised clinical study of 50 breast cancer patients who received adjuvant radio- and/or chemotherapy, there was a considerably better improvement in quality of life after only two months compared with the placebo group for supplementary mistletoe extract treatment [49]. In a prospective, randomised clinical study in 21 patients with advanced breast cancer given standardised mistletoe extracts in addition to adjuvant VEC chemotherapy, the disease- and treatment-associated symptoms and the leucopenia associated with the chemotherapy improved significantly compared with 19 control patients [50]. In a prospective, randomised, placebo-controlled study to investigate the dose-response relationship of a lectin-standardised mistletoe preparation in addition to adjuvant CMF-chemotherapy, a significant, dose-related improvement in validated quality of life criteria and lymphocyte subpopulations was reported for 272 patients who underwent surgery for breast cancer [51]. In the studies quoted, relevant therapeutic efficacy of mistletoe extract treatment was reported consistently for improvement in quality of life criteria. In view of the different methods, types of cancer and treatment regimens, conducting a prospective, randomised, clinical study on improvement of quality of life with mistletoe extract treatment would be highly recommended for further clarification and quantification.

With regard to toxicity, in the present study the mistletoe extract treatment was well tolerated, with no serious or life-threatening undesirable effects, in particular no severe allergic reactions. No tumour enhancement was observed. The incidence of systemic adverse drug reactions and local reactions at the site of injection were of the same extent and quality as in previously published clinical studies with mistletoe extracts [27–29, 52]. Consequently complementary treatment with standardised mistletoe extract in breast cancer can be regarded as safe.

5. Literature

[1] Abeloff, M. D., Lichter, A. S., Niederhuber, J. E. et al., Breast. In: Clinical Oncology, Abeloff, M. D., Armitage, J. O., Lichter, A. S. et al. (Hrsg.), S. 2051–2159. Churchill Livingstone, New York (2000)

[2] Krebs in Deutschland, Häufigkeiten und Trends, S. 1–104. Arbeitgemeinschaft Bevölkerungsbezogener Krebsregister in Deutschland; Robert Koch Institut, Berlin-Saarbrücken (2002)

[3] Kreienberg, R., Möbus, V., Alt, D., Management des Mammakarzinoms, S. 1–471. Springer Verlag, Heidelberg-Berlin etc. (1998)

[4] Eifel, P., Axelson, J. A., Costa, J. et al., National Institutes of Health Consensus Development Conference Statement: adjuvant therapy for breast cancer, November 1–3, 2000. J. Natl. Cancer Inst. **93**, 979 (2001)

[5] Goldhirsch, A., Glick, J. H., Gelber, R. D. et al., Meeting highlights: International consensus panel on the treatment of primary breast cancer. J. Clin. Oncol. **19**, 3817 (2001)

[6] Margolese, R. G., Fisher, B., Hortobagyi, G. N. et al., Neoplasms of the Breast. In: Cancer Medicine, Bast, R. C. Jr., Kufe, D. W., Pollock, R. E. et al. (Hrsg.), S. 1735–1822. B. C. Decker, Hamilton-London (2000)

[7] Partridge, A. H., Burstein, H. J., Winer, E. P., Side Effects of Chemotherapy and Combined Chemohormonal Therapy in Women With Early-Stage Breast Cancer. J. Natl. Cancer Inst. Monographs **30**, 135 (2001)

[8] Shapiro, C. L., Recht, A., Side Effects of Adjuvant Treatment of Breast Cancer. N. Engl. J. Med. **344**, 1997 (2001)

[9] Arora, N. K., Gustafson, D. H., Hawkins, R. P. et al., Impact of surgery and chemotherapy in younger women with breast cancer. Cancer **92**, 1288 (2001)

[10] Crivellari, D., Bonetti, M., Caglistone-Gertsch, M. et al., Burdens and benefits of adjuvant cyclophosphamide, methotrexate, and fluorouracil and tamoxifen for elderly patients with breast cancer: The International Breast Cancer Study Group Trial VII. J. Clin. Oncol. **18**, 1412 (2000)

[11] Ganz, P. A., Impact of tamoxifen adjuvant therapy. J. Natl. Cancer Inst. Monographs **30**, 130 (2001)

[12] Ganz, P. A., Desmond, K. A., Leedham, B. et al., Quality of life in long-term, disease-free survivors of breast cancer: a follow up study. J. Natl. Cancer Inst. **94**, 39 (2002)

[13] Holzner, B., Kemmler, G., Kopp, J. et al., Quality of life in breast cancer patients – not enough attention for long-term survivors? Psychosomatics **42**, 117 (2001)

[14] Longman, A. J., Braden, C. J., Mishel, M. H., Side effects burden, psychological adjustment, and quality of life in women with breast cancer: pattern of association over time. Oncol. Nurs. Forum **26**, 909 (1999)

[15] Ernst, E., Cassileth, B. R., How useful are unconventional cancer treatments? Eur. J. Cancer **35**, 1608 (1999)

[16] Ernst, E., Mistletoe for cancer? Eur. J. Cancer **37**, 9 (2001)

[17] Jacobson, J. S., Workman, S. B., Kronenberg, F., Research on complementary/alternative medicine for patients with breast cancer: a review of the biomedical literature. J. Clin. Oncol. **18**, 668 (2000)

[18] Schwabe, U., Paffrath, D., Arzneiverordnungsreport 2003, S. 548–550, Springer Verlag, Berlin-Heidelberg etc. (2004)

[19] Moschèn, R., Kemmler, G., Schweigkofler, H. et al., Use of alternative/complementary therapy in breast cancer patients – a psychological perspective. Support Care Cancer **9**, 267 (2001)

[20] Büssing, A., Biological and pharmacological properties of Viscum Album L. In: Mistletoe, The Genus Viscum, Büssing, A. (ed.), p. 123–183. Harwood Academic Publishers, Amsterdam (2000)

[21] Fischer, S., Scheffler, A., Kabelitz, D., Stimulation of the specific immune system by mistletoe extracts. Anticancer Drugs **8**, Suppl 1, S33 (1997)

[22] Hajto, T., Hostanska, K., Saller, R., Mistletoe therapy from the pharmacologic perspective. Forsch. Komplementärmed. **6**, 186 (1999)

[23] Stein, G. M., Toxicology of Mistletoe Extracts and their Components. In: Mistletoe, The Genus Viscum, Büssing, A. (ed.), p. 183–194. Harwood Academic Publishers, Amsterdam (2000)

[24] Kiene, H., Beurteilung klinischer Studien zur Misteltherapie. In: Grundlagen der Misteltherapie, Scheer, R., Becker, H., Berg, P. A., S. 484–496. Hippokrates Verlag, Stuttgart (1996)

[25] Kiene, H., Büschel, G., Horneber, M., Mistletoe or not mistletoe is still the question. Forsch. Komplementärmed. Klass. Naturheilkd. **8**, 309 (2001)

[26] Kleijnen, J., Knipschild, P., Mistletoe treatment for cancer: review of controlled trials in humans. Phytomedicine **1**, 255 (1994)

[27] Gorter, R. W., van Wely, M., Reif, M. et al., Tolerability of an extract of European mistletoe among immunocompromised and healthy individuals. Altern. Ther. Health Med. **5**, 37 (1999)

[28] Huber, R., Thoma, D., Klein, R. et al., Klinische Wirkungen und Nebenwirkungen eines lektinreichen (Mistelextrakt Q spezial) und eines lektinarmen (Mistelextrakt pini) Mistelpräparates – Ergebnisse einer randomisierten, placebokontrollierten Phase I Studie bei Gesunden. In: Die Mistel in der Tumortherapie – Grundlagenforschung und Klinik, Scheer, R., Bauer R. H., Becker, P. A. et al., S. 473–484. KVC Publishers, Essen (2001)

[29] Van Wely, M., Stoss, M., Gorter, R. W., Toxicity of a standardized mistletoe extract in immunocompromised and healthy individuals. Am. J. Ther. **6**, 37 (1999)

[30] Hanisch, J., Bock, P. R., Karasmann, M., Standard operating procedures and the operational manual for retrolective cohort studies according to the IFAG-standard (Retrospect^{TM}), Manual. IFAG, Basel (2000)

[31] Feinstein, A. R., Clinical Epidemiology, The Architecture of Clinical Research, S. 1–811. W. B. Saunders, Philadelphia (1985)

[32] Schneider, B., Analysis of therapeutic efficacy in observational cohort studies. Cancer Chemother. Pharmacol. **47**, 35 (2001)

[33] Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to human medicinal products. Official Journal of the European Communities L **311**, 67–128 (2001)

[34] German Cochrane Center, Evidence hierarchy. www.cochrane.de/deutsch/ccevidenzhierarchie.htm (2002)

[35] Oxford Centre for Evidence-based Medicine, Levels of Evidence and Grades of Recommendation, www.cebm.net/levels_of_evidence.asp (2001)

[36] Benson, K., Hartz, A. J., A comparison of observational studies and randomized clinical trials. N. Engl. J. Med. **342**, 1878 (2000)

[37] Concato, J., Shah, N., Horwitz, R. I., Randomized, controlled trials, observational studies, and the hierarchy of research design. N. Engl. J. Med. **342**, 1887 (2000)

[38] Feinstein, A. R., The role of observational studies in the evaluation of therapy. Stat. Med. **3**, 341 (1984)

[39] Hlatky, M. A., Califf, R. M., Harrell-Fe, J., Comparison of predictions based on observational data with the results of randomized controlled clinical trials of coronary artery bypass surgery. J. Am. Coll. Cardiol. **11**, 237 (1988)

[40] Rosati, R. A., Lee, K. L., Califf, R. M. et al., Problems and Advantages of an Observational Data Base Approach to Evaluating the Effect of Therapy on Outcome. Circulation **65**, Suppl. II, 27 (1982)

[41] Dold, U., Edler, L. H. Mäurer, C. et al., Krebszusatztherapie beim fortgeschrittenen nichtkleinzelligen Bronchialkarzinom, Multizentrische kontrollierte Studie zur Prüfung der Wirksamkeit von Mistelextrakt und Polyerga. Thieme Verlag, Stuttgart-New York (1991)

[42] Steuer-Vogt, M. K., Bonkowsky, V., Ambrosch, P. et al., The effect of an adjuvant mistletoe treatment program in resected head and neck cancer patients: a randomised controlled clinical trial. Eur. J. Cancer **37**, 23 (2001)

[43] Gutsch, J., Berger, H., Scholz, G. et al., Prospective study in radically operated breast cancer with polychemotherapy, Helixor and untreated control. Dtsch. Zschr. Onkol. **21**, 94 (1988)

[44] Grossarth-Maticek, R., Kiene, H., Baumgartner, S. M. et al., Use of Iscador, an extract of European mistletoe (Viscum album), in cancer treatment: prospective nonrandomized and randomized matched-pair studies nested within a cohort study. Altern. Ther. Health Med. **7**, 57 (2001)

[45] Lenartz, D., Dott, U., Menzel, J. et al., Survival of glioma patients after complementary treatment with galactoside-specific lectin from mistletoe. Anticancer Res. **20**, 2073 (2000)

[46] Edler, L., Randomisierte klinische Studien zur Misteltherapie bei Krebs: Ergebnisse, Erfahrungen und Perspektiven. In: Grundlagen der Misteltherapie, Scheer, R., Becker, H., Berg, P. A. Hippokrates Verlag, Stuttgart (1996)

[47] Schumacher, K., Schneider, B., Reich, G. et al., Post surgical complementary therapy of primary breast carcinoma with a lectin-standardized mistletoe extract – an epidemiological, controlled, multicenter, retrolective cohort study. German J. Oncol. **34**, 106 (2002)

[48] Finelli, A., Limberg, R., Scheithe, K., Mistel-Lektin bei Patienten mit Tumorerkrankungen. Medizin im Bild **1**, 1 (1998)

[49] Borrelli, E., Valutazione della qualità di vita in pazienti affette da adenocarcinoma mammario sottoposte a terapia con Viscum album. La Medicina Biologica **17,** 27 (1999)

[50] Heiny, B. M., Additive Therapie mit standardisiertem Mistelextrakt reduziert die Leukopenie und verbessert die Lebensqualität von Patientinnen mit fortgeschrittenem Mammakarzinom unter palliativer Chemotherapie (VEC-Schema). Krebsmedizin **12**, 1 (1991)

[51] Wetzel, D., Results of a randomized placebo-controlled multicentre study with PS76A2 (standardized mistletoe preparation) in patients with breast cancer receiving chemotherapy. Phytomedicine **7**, Suppl. 2, 34 (2000)

[52] Stein, G. M., Berg, P. A., Adverse effects during therapy with mistletoe extracts. In: Mistletoe, The Genus Viscum, Büssing, A. (Hrsg.), S. 195–208. Harwood Academic Publishers, Amsterdam (2000)

Correspondence:
Prof. Dr. Berthold Schneider,
Institut für Medizinische Statistik,
Medizinische Hochschule Hannover,
Carl-Neuberg-Str. 1,
30625 Hannover (Germany)
Fax: +49 (0)511 532 42 95
E-mail: schneider.berthold@mh-hannover.de

Editors: Prof. Dr. Hans-Georg Classen, Viktor Schramm. Secretary's Office: Christine Schäffer. Publisher: ECV · Editio Cantor Verlag für Medizin und Naturwissenschaften GmbH, P.O.B. 12 55, 88322 Aulendorf (Germany), Phone +49 (0) 7525-9400, Fax +49 (0) 7525-940 180; e-mail: redaktion@ecv.de; http://www.ecv.de. Printed by VeBu Druck + Medien GmbH, Am Reutele 18, 88427 Bad Schussenried (Germany).

Terms of supply: The journal is published monthly and can be obtained from the publisher or via bookstores. Rates per annum for the print + online subscription (VAT included, minimum 12 issues): *Germany:* 325.– € plus 15.– € postage. *Abroad (Europe* with *VAT ID number)*: 343.93 € plus 30.17 € postage (air mail: 68.96 €). *Abroad (Europe* without *VAT ID number and other countries)*: 368.– € plus 35.– € postage (air mail: 80.– €). Price for a single copy: 35.– € plus postage. Please ask for extended network licences. A subscription remains legally valid unless it is cancelled at 3 months notice for the end of the period of computation.

Printed in Germany · ISSN 0004-4172

50 608 0GB