ANTICANCER RESEARCH *38*: 1585-1593 (2018)
doi:10.21873/anticanres.12388

Is Mistletoe Treatment Beneficial in Invasive Breast Cancer? A New Approach to an Unresolved Problem

PETER FRITZ[1], JÜRGEN DIPPON[2], SIMON MÜLLER[2], SVEN GOLETZ[2], CHRISTIAN TRAUTMANN[3], XENOPHON PAPPAS[4], GERMAN OTT[1], HILTRUD BRAUCH[5], MATTHIAS SCHWAB[5,6], STEFAN WINTER[5], THOMAS MÜRDTER[5], FRIEDHELM BRINKMANN[7], SIMONE FAISST[7], SUSANNE RÖSSLE[7], ANDREAS GERTEIS[3] and GODEHARD FRIEDEL[8]

[1]*Department of Clinical Pathology, Robert Bosch Hospital, Stuttgart, Germany;*
[2]*Institute of Stochastics and Applications, University of Stuttgart, Stuttgart, Germany;*
[3]*Department of Gynecology and Obstetrics, Robert-Bosch-Hospital, Stuttgart, Germany;*
[4]*Radiologie Nuklearmedizin Winnenden, Winnenden, Germany;*
[5]*Margarete Fischer-Bosch-Institute of Clinical Pharmacology and University of Tuebingen, Stuttgart, Germany;*
[6]*Department of Clinical Pharmacology, University Hospital Tuebingen, Stuttgart, Germany;*
[7]*Onkologischer Schwerpunkt Stuttgart e.V., Stuttgart, Germany;*
[8]*Center for Pulmonology and Thoracic Surgery, Klinik Schillerhöhe, Stuttgart-Gerlingen, Germany*

Abstract. *Background/Aim: In this retrospective study, we compared breast cancer patients treated with and without mistletoe lectin I (ML-I) in addition to standard breast cancer treatment in order to determine a possible effect of this complementary treatment. Patients and Methods: This study included 18,528 patients with invasive breast cancer. Data on additional ML-I treatments were reported for 164 patients. We developed a "similar case" method with a distance measure retrieved from the beta variable in Cox regression to compare these patients, after stage adjustment, with their non-ML-1 treated counterparts in order to answer three hypotheses concerning overall survival, recurrence free survival and life quality. Results: Raw data analysis of an additional ML-I treatment yielded a worse outcome (p=0.02) for patients with ML treatment, possibly due to a bias inherent in the ML-I- treated patients. Using the "similar case" method (a case- based reasoning approach) we could not confirm this harm for patients using ML-I. Analysis of life quality data did not demonstrate reliable differences between patients treated with ML-I treatment and those without proven ML-I treatment. Conclusion: Based on a "similar case" model we did not observe any differences in the overall survival (OS), recurrence- free survival (RFS), and quality of life data between breast cancer patients with standard treatment and those who in addition to standard treatment received ML-I treatment.*

Correspondence to: Godehard Friedel, Klinik Schillerhöhe, Center for Pulmonology and Thoracic Surgery, Solitudestr. 18, 70839 Stuttgart, Germany. Tel: +49 71562037241, Fax: +49 71562037003, e-mail: godehard.friedel@klinik-schillerhoehe.de

Key Words: ML 1, breast cancer treatment, complementary medicine, prognosis.

Treatment of breast cancer is based on an elaborate decision tree, which is influenced by the patho-morphological features of breast cancer, the knowledge of the physician in charge, and the decision of the patient. Even for the well justified treatment modalities, the benefits of a certain decision are hard to measure, as revealed by Adjuvant Online (1). In addition to standard treatment, complementary therapies are also used in breast cancer, mostly at the request of the patient (2). Mistletoe lectin (ML-I) is one of the most frequently complementary treatment options (3). There are some studies (4-16) that argue ML-I treatment may be beneficial if given in addition to standard treatment. The benefits claimed for this ML-I treatment are: 1) improvement in the patient's quality of life (5, 7, 8, 10, 11, 13), 2) reduction of cancer-related fatigue or side effects of anti-cancer chemotherapy (6, 9, 14), 3) improvement of relapse free survival (RFS), and 4) improvement of overall survival (OS) (17, 18). However, seen by the perspective of patients, the problem of decision making for or against a complementary ML-I treatment in a given breast cancer are not solved. Based on a plethora of data (retrospective, prospective and scientific) the patient or the patient and the physician in charge had to do a binary (no/yes) decision.

Here, we use a new statistical approach (case-based reasoning) to analyze retrospective data (19, 20). Three hypotheses were tested: Additional ML-I treatment had no statistically significant harm or benefit on OS and RFS

(hypotheses 1 and 2). Life quality data are not different in patients treated with ML-I in addition to a conventional treatment approach.

Patients and Methods

Patients. All data were retrieved from the breast cancer data base of the OSP Stuttgart (Onkologischer Schwerpunkt Stuttgart) (19, 20). Patients were diagnosed with breast cancer from January 1, 1989- March 31, 2011. Patients (N=18,528) with invasive breast cancer were available for analysis. pT, pN, M were classified following TNM classification (Table I) (21). PN1mi was classified as pN1. The biological disease modifiers, ER (estrogen receptor), PR (progesterone receptor), and cerb-B2 were reported as immunoreactive scores (Remmele score, levels: 0-4, 6, 8, 9, and 12) (22) and cerb-b2 with levels 0-3. A breast cancer was considered ER or PR positive if the Remmele score was >1 (22). Cerb-B2 was considered positive for an immunohistochemical score of 3. The distribution of T, N, and M (as shown in Table I) was used to calculate the stage and substage following the TNM recommendation (21). Two subsets were compared in the raw data analysis: 1) ML-I Subset. These are patients with a proven ML-I treatment (N=164), and 2) NON-ML-I subset. These are all patients with breast cancer in the OSP registry without reported ML-I treatment (N=18,528-164=18364).

Similar patients were selected by a statistical approach (see below) and two collectives were analyzed following the recommendations of Austin (23). Model 1: Similarity was defined by 8 variables (Table I): pT, pN, M, age (cut-off 60 years), year of diagnosis (cut-off year=2000), chemotherapeutical treatment, anti-hormonal treatment, and radiation.

Model 2: Similarity was defined by those 4 variables which were significantly different between the 164 ML-I treated breast cancers and their counterparts without proven ML-I treatment. The variables selected for assessment of similarity were pT, pN, age, year of diagnosis.

Treatment data. The reports available contained information about: 1) chemotherapy (yes/no, not available), with yes indicating patients were treated with one or more chemotherapies without further specification; 2) radiation (yes/no, not available), with yes indicating patients treated with one or more radiation treatments without further specification; and 3) anti-hormonal treatment (yes/no, not available), with yes indicating patients received one or more anti-hormonal treatments without further specification. In addition, 164 patients received mistletoe treatment (ML-I). Different pharmacological variants were applied: Lectinol^{R}, Abnoba^{R}, Helixor^{R}, Iscador^{R}, and Aviscumine^{R} (24, 25). Our retrospective data did not allow to discriminate between these 5 treatment modalities. All other patients had either no ML-I application or this treatment was not disclosed in the medical reports (25). In a subset of patients receiving chemotherapy information about a specific treatment consisting of cyclophosphamide, methotrexate, and fluorouracil (CMF) was available. For patients receiving anti-hormonal treatment, records indicated whether this treatment was tamoxifen or an aromatase inhibitor (not further subdivided) (25).

Survival. OS was calculated from the date of diagnosis to either death or last registration. Death could only rarely be classified as either tumor-related or not tumor-related. Therefore, all causes of death were taken into consideration. For comparing non-tumor related deaths, we utilized the life table of the Federal Statistical Office of Germany (26). The RFS was defined as the time between diagnosis and either death from any cause, local relapse, or distant metastasis.

Subset analysis. Five subsets were analyzed. 1) high risk patients defined by G3 breast cancer, 2) low risk patients defined as pT1 or pT2, N0, G1 or G2, 3) patients aged >50 years, 4) patients with a CMF chemotherapy, and 5) tamoxifen treatment.

Life quality analysis. In 3633 patients a life quality assessment was performed using the EORTC QLQ-C30 version 3.0. This assessment consisted of 30 questions with an item range of mostly 3 or 6 (question 29 and 30 concerning global health status) (27, 28). For 101 patients of our case based reasoning procedure (CBR) model these life data were available. From each patient, at least, two questionnaires were available. The hypothesis tested was two sided and the level of significance was set at p=0.05. The hypothesis was that ML-I treatment has a significant influence on life quality. For eviting a false interpretation by a multiple testing approach, we performed a Bonferroni-Holm correction with n=15 (number of different tests in the scoring system of QLQ-C30). The EORTC QLQ-C30 discriminates between symptom scales (0-100) higher values signifying more intensive symptoms (decreased life quality) and functionating scales higher values signifying good life quality. We analyzed 1) the first life quality assessment, 2) the mean of life quality assessment, if more than one assessment was done, and 3) the change in the life quality scales, if more than one assessment was done, discriminating three groups: no change, increase or decrease of life quality variables. Analysis was done with model 1 or model 2 data sets separately.

Statistical analyses. The data used for analysis correspond to a retrospective study in which the total population of patients suffering from breast cancer in the area of Stuttgart is analyzed (25). The overall survival data were retrieved from the life table of the Statistische Bundesamt Deutschland (26). Data analysis was performed with R, version 3.3.2 (29) and a function written by the authors to select cases from a registry that are similar to a given case (19, 20, 30). To be more specific, as a first step this function computes the beta vector of the log hazard ratios in a Cox regression set up with the factors to be considered in the given case. In a second step, this beta vector is used to define a distance on the space of the possible values of the chosen factors. Finally, in a third step, N=3 cases out of the data set, nearest to the given case in the sense of the computed distance, are determined. The selection of the matched cases was done with replacement. By this method, for each case of a small subset from a data set, N cases from the entire data set can be matched. Then, by log-rank test, survival of the subset and the matched data set can be compared. Taken into consideration “the lack of consensus in the literature as to which variables one should include in the propensity score” we followed the recommendation (model 1) of Austin (23) to use variables with presumed prognostic effect. His second recommendation for as few variables as possible was followed in model 2. The matching procedure takes into account both the importance of the considered factors with respect to survival and the natural ordering of factor levels. The variables selected for

Table I. *Clinical and pathological findings of study patients (raw data analysis).*

Variable	Set		*p*-Value *t*-test chi-square-test	Standardized mean difference
	ML-1	Non-ML-1		
ML-1 treatment	yes	unknown		
N	164	18364		
	year	year		
Age			0.0000024	0.026
Mean	55.7	60.0		
Sd	11.0	13.3		
Median	55.1	59.9	0.0049	
>=60 years	63	9225		
<60 years	101	9139		
Missing values	0	0		
Year of diagnosis			0.03	0.186
Mean	1991.1	2003		
Sd	6.7	6.1		
Median	1991	2000	0.13	
<2000	76	7456		
>=2000	88	10908		
Missing values	0	0		
	N (%)	N (%)		
pT0	4 (2.5)	136 (0.7)	0.05	0.196
pT1	64 (40.8)	8290 (46.6)		
pT2	66 (42.0)	7134 (40.1)		
pT3	8 (5.1)	1005 (5.6)		
pT4	15 (9.6)	1203 (6.8)		
Missing values	7	596		
N0	79 (52.0)	10317 (59.7)	0.07	0.214
N1	51 (33.6)	5349 (31.0)		
N2	18 (11.8)	1177 (6.8)		
N3	4 (2.6)	434 (2.5)		
Missing values	12	1087		
M0	137 (93.8)	15852 (94.4)		
M1	9 (6.2)	946 (5.6)	0.92	0.023
Missing values	18	1566		
Stage I	49 (35.3)	6002 (36.8)	0.92	0.061
Stage II	61 (43.8)	7295 (44.7)		
Stage III	20 (14.4)	2068 (12.7)		
Stage IV	9 (6.5)	946 (5.8)		
Missing values	25	2053		
G1	14 (9.3)	1707 (10.6)	0.33	0.112
G2	91 (60.3)	10387 (64.3)		
G3	46 (30.4)	4070 (25.1)		
Missing values	13	2200		
ER-negative	40 (28.6)	3778 (23.5)	0.19	0.105
ER-positive	100 (71.4)	12315 (76.5)		
Missing values	24	2271		
PR negative	53 (37.9)	5229 (32.6)	0.22	0.044
PR positive	87 (62.19)	10808 (67.4)		
Missing values	24	2027		
cerbB2*-negative	49 (86.0)	6347 (85.2)	1	0.034
cerbB2-positive	8 (14.0)	1106 (14.8)		
Missing values	107	10911		
Chemo no	89 (54.3)	10566 (57.5)	0.45	0.066
Chemo yes	75 (45.7)	7798 (42.5)		
Missing values	0	0		
Anti-hormonal no	82 (50.0)	8702 (47.4)	0.56	0.052
Antihormonal yes	82 (50.0)	9662 (52.6)		
Missing values	0	0		
Radiation no	54 (32.9)	6201 (33.8)	0.89	0.018
Radiation yes	110 (67.1)	12163 (66.2)		
Missing values	0	0		

*Scores of 0-2 are considered negative.

Table II. *Comparison of case based reasoning data. Similar cases were chosen for statistical ($p<0.05$) and biological reasons (clinical or statistical relevance of the matched variable should be given).*

Variable	Set		*p*-Value *t*-test (Wilcoxon-test) chi-square test	Standardized mean difference
	ML-1	Non-ML-1 Model 1		
ML-1 treatment	yes	unknown		
N	141	423		
	year	year		
Age				
Mean	55.3	57.6	0.04 (0.11)	0.064
Sd	11.3	12.6		
Median	55.1	55.9		
≥60 years	53 (37.6)	166 (39.2)	0.8	
<60 years	88 (62.4)	267 (60.8)		
Missing values	0	0		
Year of diagnosis			0.26 (0.27)	0.114
Mean	1999.2	1999.7		
Sd	6.9	6.2		
Median	1999	1999		
<2,000	78 (55.3)	229 (54.1)		
≥2000	63 (44.7)	194 (45.9)	0.89	
Missing values	0	0		
	N (%)	N (%)		
pT0	4 (2.8)	12 (2.8)	0.99	0.025
pT1	60 (42.6)	181 (42.8)		
pT2	60 (42.6)	180 (42.6)		
pT3	6 (4.2)	16 (3.8)		
pT4	11 (7.8)	34 (8.0)		
Missing values	0	0		
N0	76 (53.9)	228 (53.9)	0.96	0.073
N1	49 (34.7)	148 (35.0)		
N2	12 (8.5)	38 (9.0)		
N3	4 (2.9)	9 (2.1)		
Missing values	0	0		
M0	134 (95.0)	400 (94.6)	1	0.021
M1	7 (5.0)	23 (5.4)		
Missing values	0	0		
Stage I	49 (35.8)	144 (35.0)	0.99	0.026
Stage II	61 (44.5)	185 (45.0)		
Stage III	20 (14.6)	59 (14.4)		
Stage IV	7 (5.1)	23 (5.6)		
Missing values	4	12		
G1	13 (10.1)	26 (6.8)	0.45	0.053
G2	80 (62.0)	252 (65.6)		
G3	36 (27.9)	106 (27.6)		
Missing values	12	39		
ER-negative	35 (27.8)	115 (29.6)	0.78	0.067
ER-positive	91 (72.2)	274 (70.4)		
Missing values	15	34		
PR-negative	48 (38.1)	136 (35.8)	0.72	0.053
PR-positive	78 (61.9)	244 (64.2)		
Missing values	15	43		
cerbB2*-negative	44 (84.6)	137 (78.7)	0.46	0.305
cerbB2-positive	8 (15.4)	37 (21.3)		
Missing values	89	249		
Chemo no	74 (52.5)	219 (51.8)	0.96	0.014
Chemo yes	67 (47.5)	204 (48.2)		
Missing values	0	0		
Anti-hormonal no	70 (49.6)	211 (49.9)	1	0.005
Anti-hormonal yes	71 (50.4)	212 (50.1)		
Missing values	0	0		
Radiation no	43 (30.5)	129 (30.5)	1	<0.001
Radiation yes	98 (69.5)	294 (69.5)		
Missing values	0	0		

choosing similar cases are: pT, pN, M, age (cut-off 60 years), year of diagnosis (cut-off year=2000), chemotherapeutic treatment, anti-hormonal treatment, and radiation (model 1). In model 2 pN, pT, age and year of diagnosis entered the model.

To judge the power of our study, we recall that the relation of subset size of proven and non-proven ML-I treatment cases was 1:3, and the 10-year survival rate in the non-proven ML subset was 0.55. If we request a power of 0.8, the number of events needed is 267/499/1172 to prove that 10-year survival in the proven ML-I subset is increased by 20%/15%/10% (event size calculation according to Collett (31). However, due to censoring we must include even more cases. Supposing that recruiting and follow-up time each equals 10 years, the total sample sizes mount up to 491/898/2071, respectively.

We used the *t*-test, the Wilcoxon-test and the statistical mean difference for comparison of numerical data, and the chi-square test or fisher test for categorical data. Statistical hypothesis test is not considered as a valid tool to check the balance of matched data. Nevertheless, for sake of convenience we included *p*-values in an additional column. The effect size (mean statistical difference) was considered to be small (<0.2), medium (0.2-0.49) or large (≥0.5) (32). Differences in survival were analyzed with the log-rank test and the Cox survival test. *p*-Values less than 0.05 were considered statistically significant and $p<0.001$ as highly significant. *p*-Values less than 10^{-6} were termed $p=0$.

Results

Patients: We first analyzed the population of all breast cancer patients of a south-western region in Germany and divided it into two subsets (1) breast cancer patients treated with ML-I and (2) those without a reported ML-I treatment (not-ML-I treated) (Table I). Most patients were classified as stage I or II invasive breast cancer, ER or PR positive, and cerb-B2 negative. However, the ML-I treated subset showed significantly more patients with higher pT and pN. The mean age of the ML-I treated patients was 55.7 years (median 55.1, sd=11.0, inter quantile range (IQR)=15.41, range=29.2-81.0 years) *versus* 60.0 years (median=59.9, sd=13.3, IQR=19.07, range=18.2-101.4 years) for the Non-ML-I treated patient group. The ML-I treated patients were approximately 4 years younger than the whole population ($p=0$). Therefore, both subsets, the large without reported ML-I treatment (N=18,364) and the small one with reported ML-I treatment (N=164) are highly biased. A direct comparison between both subsets in Table I is hampered by many biases as shown by the standardized mean difference or statistically significant different distributions of age, pT, year of diagnosis and pN. Concerning the treatment data (raw data, Table I) ML-I treated patients and those without a reported ML-I treatment had no statistical difference. After selecting the similar case patients either with model 1 or 2 we found no differences between the subsets of ML-I treated patients and their most similar counterparts (Tables II and III) based on the statistical mean difference.

Table III. *Comparison of case based reasoning data. Similar cases were chosen for statistical (p<0.05) reasons only.*

Variable	Set		*p*-Value t-test (Wilcoxon-test) chi-square test	Standardized mean difference
	ML	Non-ML Model 2		
ML-1 treatment	yes	unknown		
N	151	453		
	year	year		
Age			0.82 (0.89)	0.042
Mean	55.5	55.7		
Sd	11.2	11.8		
Median	55.1	55.2		
>=60 years	58 (38.4)	174 (38.4)	0.68	
<60 years	93 (61.6)	279 (61.6)		
Missing Values	0	0		
Year of diagnosis			0.51 (0.52)	0.026
Mean	1999.2	1999.6		
Sd	6.8	6.8		
Median	1999	1999		
<2000	86 (57.0)	247 (54.5)		
>=2000	65 (43.0)	206 (45.5)	0.68	
Missing values	0	0		
	N (%)	N (%)		
pT0	4 (2.6)	9 (2.0)	0.97	0.033
pT1	64 (42.4)	193 (42.6)		
pT2	62 (41.1)	185 (40.8)		
pT3	8 (5.3)	21 (4.6)		
pT4	13 (8.6)	45 (9.9)		
Missing values	0	0		
N0	78 (51.7)	230 (50.8)	0.82	0.064
N1	51 (39.8)	160 (35.3)		
N2	18 (11.9)	50 (11.0)		
N3	4 (2.6)	13 (2.9)		
Missing values	0	0		
M0	134 (95.0)	392 (93.8)	0.73	0.086
M1	7 (5.0)	26 (6.2)		
Missing values	10	35		
Stage I	49 (35.8)	141 (34.4)	0.93	0.102
Stage II	61 (44.5)	177 (43.3)		
Stage III	20 (14.6)	65 (15.9)		
Stage IV	7 (5.1)	26 (6.4)		
Missing values	14	44		
G1	13 (9.4)	31 (7.9)	0.77	0.125
G2	87 (62.6)	258 (65.6)		
G3	39 (38.0)	104 (26.5)		
Missing values	12	60		
ER-negative	38 (28.4)	83 (21.0)	0.1	0.014
ER-positive	96 (71.6)	313 (79.0)		
Missing values	17	60		
PR-negative	51 (38.1)	126 (32.0)	0.24	0.017
PR-positive	83 (61.6)	268 (68.0)		
Missing values	17	59		
cerbB2*-negative				
Negative	46 (85.2)	141 (82.0)	0.74	0.172
Positive	8 (14.8)	31 (31.0)		
Missing values	97	281		
Chemo no	81 (53.6)	237 (52.3)	0.85	0.013
Chemo yes	70 (56.4)	216 (47.7)		
Missing values	0	0		
Anti-hormonal no	74 (49.0)	215 (47.5)	0.81	0.013
Anti-Hormoal yes	77 (51.0)	238 (52.5)		
Missing values	0	0		
Radiation no	47 (31.1)	154 (34.0)	0.58	0.024
Radiation yes	104 (68.9)	299 (66.0)		
Missing values	0	0		

Table IV. *Effects of ML-1 treatment on survival of breast cancer patients.*

ML treatment in COX survival model	Kind of analysis	*p*-Value	95%CI-intervall	Commentary (with respect to overall survival)
ML-1 all stages	Raw data	0.021	1.0-1.2	ML-1 is detrimental
ML-1 and stage	Standard			
Stage I		0.88	0.34	No effect of ML-1
Stage II		0.05	1.0-2.2	ML-1 is detrimental
Stage III		0.04	1.0-3.2	ML-1 is detrimental
Stage IV		0.78	0.4-2.1	No effect of ML-1
ML-1 all stages	Model-1	0.99	0.72-1.4	No effect of ML-1
ML-1 and stage	Model-1			
Stage I		0.29	0.23-1.55	No effect of ML-1
Stage II		0.19	0.86-2.14	No effect of ML-1
Stage III		0.39	0.7-2.6	No effect of ML-1
Stage IV		0.64	0.25-2.3	No effect of ML-1
ML-1 all stages	Model-2	0.50	0.66-1.22	No effect of ML-1
ML-1 and stage	Model-2			
Stage I		0.56	0.28-2.0	No effect of ML-1
Stage II		0.88	0.62-1.5	No effect of ML-1
Stage III		0.54	0.64-2.32	No effect of ML-1
Stage IV		0.62	0.27-2.20	No effect of ML-1

Survival analysis. When we analyzed the survival difference between patients treated (ML-I group) and not treated with ML-I (Non-ML-I group) in the raw data population, we found a harmful effect for the ML-I treated patients (95%CI-interval=1-1.2, p=0.02) (Table IV, Figure 1) with regard to survival. When we analyzed the data in a stage-adjusted manner, the harmful effects of the ML-I treatment were determined in stage II (95% CI-interval=1-2.2, p=0.05) and III (95%CI-interval=1-3.2, p=0.04) (Table IV).

When we repeated the survival analysis using a similar case approach, this disadvantage disappeared (Figure 2 and Table IV) independent of the choice of variables (model 1 and 2). Adding stage to the Cox analysis (Table IV) confirmed this result. In model 1 population, similarity was defined on the basis of T, N, M, age (cut-off= 60 years), year of diagnosis (cut-off=year of diagnosis 2000), chemotherapy, anti-hormonal treatment and radiation. The 5-year survival, for example, was 75.1% (95%CI=67.6-83.3) in the ML-I treated subset (Table II and Figure 1) and 78.4% (95%CI=74.4-82.6) in the similar subset. For comparison, a woman aged 60 years without breast cancer has a 5-year survival of 96.9% ("Überlebensdaten Statistisches Bundesamt" 2009/201) (26). There were no significant differences in the RFS (p=0.4), when comparing ML-I treated with "not-treated" patients. When we repeated the analysis with the similar case group chosen by model 2 the results did not change (Table IV).

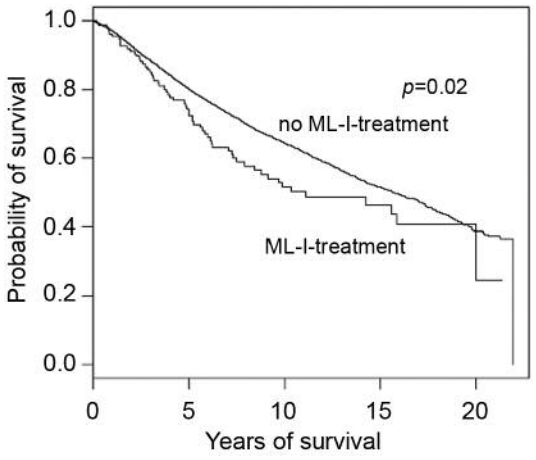

Figure 1. *Comparison of patients with ML-I treatment to those without reported ML-I treatment (raw data).*

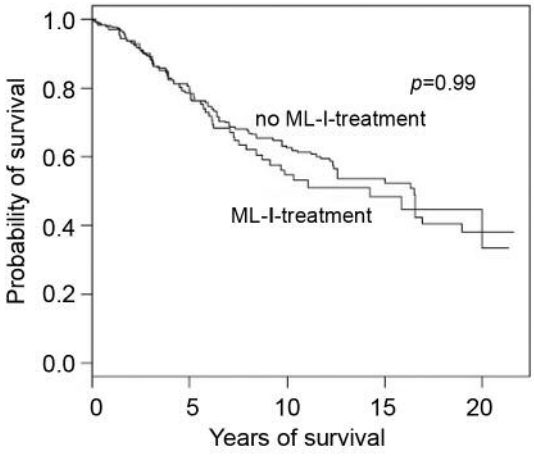

Figure 2. *Comparison of patients with ML-I treatment to those without reported ML-1 treatment (analysis with matched data).*

Life quality analysis. A total of 101 out of 604 patients (13.1%) provided data for evaluation of life quality (Table V) (27, 28). Physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning were not affected by an additional ML-I treatment (Tables V and VI). This holds true for analysis of the first life quality assessment or the mean of life quality assessments. If we analyzed the proportion of patients with increasing life quality in the global health scale, we observed non-improved health life quality (p=0.82). All other variables (symptoms or scales) did not show statistically significant differences between the ML-1 and Non-ML-1 treated patient groups (Table VI).

Table V. *Life quality functionating scales in ML-1-treated and non-ML-1-treated patients.*

Variable	Abbr	ML-1	Non-ML-1	*p*-Value
Physical functionating	PF2			
First evaluation median		76.5	80	0.4
Interquantile		27	26	
Median of all evaluations		75.3	80.7	0.14
Interquantile		22.7	14	
Increase N (%)		6/23 (26.1)	21/77 (27.3)	1
Role functionating	RF2			
First evaluation median		50	67	0.61
Interquantile		45.8	37.3	
Median of all evaluations		60.3	66.7	0.23
Interquantile		38.8	25	
Increase N (%)		4/22 (18.2)	12/77 (15.6)	1
Emotional functionating	EF			
First evaluation median		58	75	0.31
Interquantile		39.5	42	
Median of all evaluations		65.9	73.3	0.40
Interquantile		31.1	25.9	
Increase N (%)		5/21 (23.8)	32/75 (42.7)	0.19
Cognitive functionating	CF			
First evaluation median		83	83	0.61
Interquantile		33	17	
Median of all evaluations		83.3	88.3	0.72
Interquantile		36.8	28.3	
Increase N (%)		6/23 (26.1)	33/77 (42.9)	0.23
Social functionating	SF			
First evaluation median		67	83	0.16
Interquantile		41.5	33	
Median of all evaluations		66.7	75	0.33
Interquantile		28.5	30	
Increase N (%)		5/23 (21.7)	28/77 (36.4)	0.29
Global health status	QI2			
First evaluation median		50	66.7	0.23
Interquantile		25	25	
Median of all evaluations		62.5	66.7	0.5
Interquantile		21.6	22.5	
Increase N (%)		8/23 (34.8)	31/77 (40.3)	0.82

Interpretation: life quality functionating scales range between 0-100. A high life function scale signifies a good life quality. No differences in life quality were observed between ML-I treated and Non-ML-I patient groups in the functionating scale.

Subset analysis (ML-I treated patients versus Non-ML-I treated patients) in model 1 and 2. If we analyzed only patients treated with tamoxifen or CMF, we found no statistically significant harm for the additional ML-I treated patients (p=0.98, respectively p=0.31). The same holds true for the G1, G2 and G3 subsets (p=0.10, p=0.44, respectively p=0.27), the low and high-risk group (p=0.33, respectively 0.29).

Table VI. *Symptoms scales of life quality variables in ML-1 treated and non-ML-1 treated patients.*

Variable	Abbr	ML-1	Non-ML-1	*p*-Value
Fatigue	FA			
First answer median		44	44	0.59
Interquantile		45	45	
Median		38.9	–37.8	0.32
Interquantile		31.1	32.3	
Increase of life quality N (%)		6/23 (26.1)	20/77 (26.0)	1
Nausea and vomiting	NV			
First answer median		0	0	0.32
Interquuantile		17	0	
Median		0	0	0.76
Interquantile		15.5	8.3	
Increase		1/22 (4.5)	16/77 (20.8)	0.14
Pain	PA			
First answer median		33	17	0.30
Interquantile		41.5	50	
Median		25	23.3	0.64
Interquantile		25.8	41.7	
Increase		5/23 (21.7)	19/77 (24.7)	1
Dyspnea	Dy			
First answer median		33	0	0.15
Interquantile		67	33	
Median		33.3	16.7	0.17
Interquantile		46.7	33.3	
Increase		6/23 (26.1)	20/77 (26.0)	1
Insomnia	SL			
First answer median		33	–3	0.72
Interquantile		67	33	
Median		33.3	33.3	0.74
Interquantile		55	23.3	
Increase		42/23 (8.7)	17/77 (22.1)	0.26
Appatite loss	AP			
First answer median		0	0	0.20
Interquantile		33	33	
Median		0	0	0.26
Interquantile		25	10	
Increase		1/22 (4.4)	12/77 (15.6)	0.29
Constipation	CO			
First answer median		0	0	0.50
Interquantile		0	33	
Median		0	0	0.97
Interquantile		29.2	28.0	
Increase		3/22 (13.6)	13/77 (16.9)	0.97
Diarrhea	DI			
First answer median		0	0	0.89
Interquantile		0	0	
Median		0	0	0.30
Interquantile		3.4	10	
Increase		1/23 (4.4)	10/77 (13.0)	0.43
Financial difficulties	FI			
First answer median		0	0	0.71
Interquantile		33	33	
Median		0	33.3	0.23
Interquantile		6.7	26.7	
Increase		2/23 (8.7)	12/77 (15.6)	0.62

Interpretation: symptoms scales range between 0-100. A high symptom scale signifies more or more intensive symptoms. No differences of life quality were observed between ML-I treated and Non-ML-I patient groups in the symptom scales.

Discussion

ML-I is a proven toxin with distinct biological effects on the immune system (33-36) and tumor cells, including triggering off necrosis and apoptosis (37). The A chain inhibits protein synthesis at the ribosomal level and the A and B chains have different immunological effects (38-40). In addition, ML-I has been shown to bind to breast cancer cells in paraffin sections (41).

According to Fasching and coworkers (10), 48.7% of patients with breast cancer receive a complementary treatment, including ML-I. Therefore, we selected three similar cases for each ML case, assuming that 75% of non-ML1 patients did not receive complementary treatment.

As many oncologists (42, 43) argue against the use of cancer patient data in retrospective studies investigating treatment modalities as there are many unknown data biases and a high number of missing values we analyzed our data in two ways (1) raw data analysis and (2) data analysis with a case based reasoning procedure.

In the first approach, we compared the whole set of patients treated with ML-I (in addition to conventional treatment) (see Table I and Figure 1) with those without a reported ML-I treatment. We found a significant disadvantage for the addition of ML-I treatment. However, this approach has to be strongly criticized due to many missing values, unknown bias, and changing treatment modalities over time, factors which may corrupt the results of the data analysis. This comparison is therefore worthless for clinical decision making. For example, the ML-I patients were four years younger than their counterparts without a documented ML1 treatment.

Based on these shortcomings of the first approach, we developed a second method (matching), where three similar cases with the same or very similar features in regards to T, N, M, age, chemotherapeutical- anti-hormonal treatment, radiation, year of diagnosis were identified for each case of breast cancer treated with ML-I. With this new approach, we did not find any benefit or harm of ML-I treatment with concern to OS (Figure 2 and Table IV), RFS or for any of the subsets studied. The strategy for selecting variables for the CBR was based on at least one of two criteria: (1) a statistical significant difference in the variables mentioned in Table I, and (2) a probable clinical impact of a variable on the course of the disease. The results of the survival analysis did not differ (Table IV) irrespective whether model 1 or model 2 data were used for the Cox regression analysis.

Concerning life quality data an additional ML-I treatment had also no influence on the assessment of life quality questionnaire, independent from whether symptom scales or functionating scales were analyzed (Tables V and VI).

What may be the medical impact of case based reasoning in breast cancer treatment? Two recent medical concepts make it worthwhile to develop better tools for retrospective data analysis:1) personalized medicine, and 2) shared decision making (43). The first concept means that each treatment decision should be governed by more patient data than those contained in the TNM system and the biological prognosis factors. The second concept means that the patient should be part of the decision making approach, which makes it necessary to provide the patient with more information about her possible disease outcome. One patient with breast cancer may ask whether she should have a distinct additional treatment such as ML-I. The use of a database with a given number of similar cases, some with the additional treatment and most without, will help to answer this question. For the concept of shared decision making, we have to provide data enabling the patient (with assistance of her physician) to make better treatment decisions, not based on the belief of either the patient, the physician, or both in a situation where no high standard prospective studies are available covering the individual situation of a given patient. Our method of similar case analysis delivers data-driven decision support.

Before drawing any conclusions from our data, the shortcomings of our approach have to be underlined. Patients with reported ML-I treatment are very infrequent in our study. Data from publications estimate that the proportion of complementary treatment in breast cancer is as high as 48.7% to 53%, with ML-I treatment being one of the most preferred options (46%) (10, 44, 45, 46). This means that up to 22% of all breast cancer patients choose a complementary ML-I treatment of their breast cancer. A further disadvantage of our study may be that our selection method for similar cases is not optimal. Three fundamental arguments should be considered in addition: (1) our CBR procedure match the control cases with replacement, (2) control cases and cases with additional ML-I treatment cases were compared by t-test or chi square test, a method being criticized by Imai and coworkers (47), and (3) the interactions of the covariables are not taken into consideration. For all three restrictions of the CBR model improvement are currently under work.

For the hypothesis tested, analysis of our data using the similar case method did not hint towards a survival or life quality benefit or harm in the ML-I patients and their non-ML-1 treated counterparts. However, the ongoing discussion about the benefits of additional ML-I treatment against the background of the undisputed biological effects of this substance (48-50, for review 50) can probably not be resolved by classical study approaches as shown by many different approaches in the past (51-52). Therefore, our approach can be considered as a data-driven hint, when a patient asks for a complementary ML-I treatment.

From our data analysis a patient or physician cannot conclude, that an additional ML treatment of breast cancer provides harm or benefit in disease outcome (RS or OVS) or life quality. Our analysis is in accordance with a recent

patient cohort study of Tröger and coworkers (53) where ML-I treatment did not influence RFS.

Acknowledgements

This research was supported by the Robert Bosch Foundation, the Sabine-Dörges-Stiftung für krebskranke Kinder, Jugendliche und junge Erwachsene. The Authors thank the radiotherapists: Prof. Dr. Schmidt (Katharinen-Hospital Stuttgart, Germany), Prof. Dr. Metzger, and Prof. Dr. Hehr (Marienhospital, Stuttgart, Germany), the surgeons: PD Dr. Hoffmann (Marienhospital), Prof. Dr. Karg (Klinikum Stuttgart), and the doctors, Kuhn and Beldermann (Karl-Olga-Hospital, Stuttgart, Germany) for providing the data.

References

1 Adjuvant-online, www.adjuvantonline.com (2014).
2 Horneber M, Bueschel G, Dennert G, Less D, Ritter E and Zwahlen M: How many patients use complementary and alternative medicine: a systematic review and metaanalysis. Integr Cancer Ther *11*: 187-203, 2012.
3 Horneber MA, Bueschel G, Huber R, Linde K and Rostock M: Mistletoe therapy in oncology. Cochrane Database Syst Rev *2*: CD003297, 2008.
4 Gutsch J: Außergewöhnlicher Krankheitsverlauf bei metastasierendem Mammakarzinom unter Misteltherapie nach pseudoallergischer Reaktion. *In*: Die Mistel in der Tumortherapie. Grundlagenforschung und Klinik. Scheer R, Bauer R, Becker H, Berg PA and Fintelmann V (eds.). KVC Verlag, Essen, pp. 379-387, 2001.
5 Schumacher K, Schneider B, Reich G, Stiefel T, Stoll G, Bock PR, Hanisch J and Beuth J: Influence of postoperative complementary treatment with lectin-standardized mistletoe extract on breast cancer patients. A controlled epidemiological multicentric retrospective cohort study. Anticancer Res *23*: 5081-5087, 2003.
6 Kienle GS, Berrino F, Büssing A, Portalupi E, Rosenzweig S and Kiene H: Mistletoe in cancer – a systematic review on controlled clinical trials. Eur J Med Res *8*: 109-119, 2003.
7 Piao BK, Wang YX, Xie GR, Mansmann H, Beuth J and Lin HS: Impact of complementary mistletoe extract treatment on quality of life in breast, ovarian and non-small lung cancer cancer patients. A prospective randomized controlled clinical trial. Anticancer Res *24*: 303-309, 2004.
8 Semiglasov VF, Stepula VV, Dudov A, Lehrmacher W and Mengs U: The standardised mistletoe extract PS76A2 improves QoL in patients with breast cancer receiving adjuvant CMF chemotherapy: a randomised placebo-controlled, double-blind, multicentric clinical trial. Anticancer Res *24*: 1293-1302, 2004.
9 Lange-Lindberg AM, Velasco Garrido M and Busse R: Mistletoe treatments for minimising side effects of anticancer chemotherapy. GMS Health Technol Assess *2*: Doc18, 2006.
10 Fasching PA, Thiel F, Nicolaisen-Murmann K, Rauh C, Engel J Lux MP, Beckmann MW and Bani MR: Association of complementary methods with quality of life and life satisfaction in patients with gynecologic and breast malignancies. Support Care Cancer *15*: 1277-1284, 2007.
11 Kienle GS and Kiene H: Complementary cancer therapy: a systematic review of prospective clinical trials on anthroposophic mistletoe extracts. Eur J Med Res *12*: 103-119, 2007.
12 Beuth J, Schneider B and Schierholz JM: Impact of complementary treatment with the standardized mistletoe extract during aftercare: a controlled multicenter comparative epidemiological cohort study. Anticancer Res *28*: 523-527, 2008.
13 Kienle GS, Glockmann A, Schink A and Kiene H: Viscum album L. extracts in breast and gynaecological cances: a systematic review of clinical and preclinical research. J Exp Clin Cancer Res *28*: 79, 2009.
14 Kienle GS and Kiene H: Influence of Viscum album L (European mistletoe) extracts on quality of life in cancer patients: a systematic review of controlled clinical studies. Integr Cancer Ther *9*: 142-157, 2010.
15 Eisenbraun J, Scheer R, Kröz M, Schad F and Huber R: Quality of life in breast cancer patients during chemotherapy and concurrent therapy with a mistletoe extract. Phytomedicine *18*: 151-157, 2011.
16 Tröger W, Zdrale Z, Tisma N and Matijasevic M: additional therapy with a mistletoe product during adjuvant chemotherapy of breast cancer patients improves quality of life: an open randomized clinical pilot trial. Evid Based Complement Alternat Med *2014*: 430518, 2014.
17 Grossarth-Maticek R and Ziegler R: Randomized and non-randomized prospective controlled cohort studies in matched pair design for the long-term therapy of breast cancer patients with a mistletoe preparation (Iscador): a re-analysis. Eur J Med Res *11*: 485-495, 2006.
18 Grossarth-Maticek R and Ziegler R: Prospective controlled cohort studies on long-term therapy of breast cancer patients with a mistletoe preparation (Iscador). Forsch Komplementmed *13*: 285-292, 2006.
19 Dippon J, Fritz P and Kohler M: A statistical approach to case based reasoning with application to breast cancer data. Comput Stat Data Anal *40*: 570-602, 2002.
20 Klenk S, Dippon J, Fritz P and Heidemann G: Interactive survival analysis with the OCDM system: From development to application. Inf Syst Front *11*: 391-403, 2009.
21 Wittekind C and Meyer JM: TNM. Klassifikation maligener Tumoren. 6. Und 7. Auflage, Wiley –Blackwell, Auflage, 2010.
22 Remmele W and Stegner HE: Recommendation for uniform definition of an immunoreactive score (IRS) for immuno-histochemical estrogen receptor detection (ER-ICA) in breast cancer tissue. Pathologe *8*: 138-140, 1987.
23 Austin PC: The use of propensity score methods with survival or time-to-event outcomes: reporting measures of effect similar to those used in randomized experiments. Stat Med *33*: 1242-1258, 2014.
24 Schöffski P, Riggert S, Fumoleau P, Campone M, Bolte O, Marreaud S, Lacombe D, Baron B, Herold M, Zwierzina H, Wilhelm-Ogubiyi K, Lentzen H and Twelves C, European Organization for Research and treatment of Cancer New Drug Development Group: Phase I trial of intravenous aviscumine (rViscumin) in patients with solid tumors: a study of the European Organization for Research and Treatment of Cancer New Drug Development Group. Ann Oncol *15*: 1816-1824, 2004.
25 Trautmann C: Retrospektive Datenanalyse anhand von Therapiedaten zum Mammakarzinom des onkologischen Schwerpunkts Stuttgart. Medical thesis. University of Tuebingen, 2012.

26 Statistisches Bundesamt Deutschland. https://www.destatis.de
27 EORTC-QLQ-C30 http://groups.eortc.be/qol/sites/default/files/img/slider/specimen_qlq-c30_english.pdf 2015.
28 Ilin E: Neurotoxizität und Langzeitauswirkung auf die Lebensqualität durch adjuvante Taxantherapie bei Mammakarzinom. Medical thesis. University of Tuebingen, 2012.
29 R Core Team: R: A language and environment for statistical computing. R Foundation for Statistical Computing, URL http:www.R-project.org 2014.
30 http://sipemu.github.io/case-based.reasoning/index.html
31 Collett D: Modelling Survival Data in Medical Research. 2nd ed., Chapman &Hall, 2003.
32 Austin PC: Balance diagnostic for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med *28*: 3083-3107, 2009.
33 Beuth J, Ko HL, Gabius HJ, Burrichter H, Oette K and Pulverer G: Behavior of lymphocyte subsets and expression of activation markers in response to immunotherapy with galactoside-specific lectin from mistletoe in breast cancer patients. Clin Invest *70*: 658-661, 1992.
34 Beuth J, Stoffel B, Ko HL, Buss G, Tunngal L and Pulverer G: Immunoactive effects of various lectin-1 dosages in mammary carcinoma patients. Arzneimittelforschung *45*: 505-507, 1995.
35 Büssing A, Stumpf C, Tröger W and Schietzel M: Course of mitogen-stimulated T lymphocytes in cancer patients treated with Viscum album extracts. Anticancer Res *27*: 2903-2910, 2007.
36 Heiny BM, Albrecht V and Beuth J: Correlation of immune cell activities and beta- endorphin release in breast carcinoma patients treated with galactose-specific lectin standardized mistletoe extract. Anticancer Res *18*: 583-586, 1998.
37 Stein G, Henn W, von Laue H and Berg P: Modulation of the cellular and humoral immune responses of tumor patients by mistletoe therapy. Eur J Med Res *3*: 194-202, 1998.
38 Pae HO, Seo WG, Oh GS, Shin MK, Lee HS, Lee HS, Kim SB and Chung HT: Potentiation of tumor necrosis factor-alpha-induced apoptosis by mistletoe lectin. Immunopharmacol Immunotoxicol *22*: 697-709, 2000.
39 Franz H: Mistletoe lectins and their A and B chains. Oncol *43*: 23–34, 1986.
40 Schumacher U, Stamouli A, Adam E, Peddie M and Pfüller U: Biochemical, histochemical and cell biological investigations on the actions of mistletoe lectins I, II, and III with human breast cancer cell lines. Glycoconj J *12*: 250-257, 1995.
41 Fritz P, Dippon J, Kierschke T, Siegle I, Möhring A, Moisa A and Mürdter TE: Impact of mistletoe lectin in breast cancer. Anticancer Res *24*: 1187-1192, 2004.
42 Aulitzky W and Becker G: Aufbau klinischer Krebsregister. Der Onkologe *17*: 115-120, 2011.
43 Windeler J, Lauterberg J, Wieseler B, Sauerland S and Lange S: Patientenregister für die Nutzenbewertung. Kein Ersatz für randomisierte Studien. Deutsches Ärzteblatt *114*: A783-6, 2017.
44 Barry MJ and Edgman-Levitan S: Shared decision making-The pinnacle of patient-centered care. N Engl J Med *306*: 780-781, 2012.
45 Nilsson J, Kallman M, Östlund U, Holgersson G, Bergqvist M and Bergström S: The use of complementary and alternative medicine in Scandinavia. Anticancer Res *36*: 3243-3251, 2016.
46 Schönekaes K, Micke O, Mücke R, Büntzel J, Glatzel M, Bruns F and Kisters K: Use of complementary/alternative therapy methods by patients with breast cancer. Forsch Komplementarmed Klass Naturheilk *10*: 304-308, 2003.
47 Imai K, King G and Stuart EA: Misunderstandings between experimentalists and observationalist about casual interference. Z R Statist Soc A *171*: 481-502, 2008.
48 Hajto T, Hostanska K and Gabius HJ: Modulatory potency of the beta-galactoside-specific lectin from mistletoe extract (Iscador) on the host defense system *in vivo* in rabbits and patients. Cancer Res *49*: 4803-4808, 1989.
49 Kröz M, Schad F, Matthes B, Pickartz H and Girke M: Blood and tissue eosinophilia, mistletoe lectin antibodies and quality of life in a breast cancer patient undergoing intratumoral and subcutaneous mistletoe lectin therapy. Forsch Komplementarmed Klass Naturheilkd *9*: 160-167, 2002.
50 Scheer R, Bauer R, Becker H, Berg PA and Fintelmann V: Die Mistel in der Tumortherapie. Grundlagenforschung und Klinik KVC, Essen, 2001.
51 Gerhard I, Abel U, Loewe-Mesch A, Huppmann S and Kuehn JJ: Problems of randomized studies in complementary medicine demonstrated in a study on mistletoe treatment of patients with breast cancer. Forsch Komplementarmed Klass Naturheilkd *11*: 150-157, 2004.
52 Kienle SG and Kienle H: Die Mistel in der Onkologie. Fakten und konzeptionelle Grundlagen. Detaillierte Darstellung der einzelnen Studien. Schattauer Verlag, pp. 552-556, 2003.
53 Tröger W, Zdrale Z and Stankovic N: 5-Jahres-Nachbeobachtung von Patientinnen mit Brustkrebs nach einer randomisierten Studie mit *Viscum-album* (L) Extrakt. Deutsche Zeitschrift für Onkologie *48*: 105-110, 2016.

Received December 11, 2017
Revised January 16, 2018
Accepted January 17, 2018