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Impact of complementary oral enzyme application on the postoperative treatment results of breast cancer patients – results of an epidemiological multicentre retrolective cohort study

Abstract *Purpose*: To evaluate the impact of postoperative treatment with an oral enzyme (OE) preparation given complementary to an antineoplastic therapy in patients with breast cancer. *Methods*: The design of this epidemiological study was a retrolective cohort analysis with parallel groups. Design and conduct of the study were performed to current standards for prospective, controlled clinical trials. A cohort of 2339 breast cancer patients undergoing surgical intervention and radio-, chemo- or hormonal therapy were studied in 216 centres. Of the 2339 patients, 1283 received complementary treatment with OE and 1056 did not receive OE. Patients with other complementary medications were excluded and the final analysis was performed with the data from 649 patients, of whom 239 (37%) were additionally treated with OE (test group) and 410 (63%) without OE (control group). The median follow-up time for the test group was 485 days and for the control group 213 days. The primary endpoint of the study was to determine whether complementary treatment with OE can reduce typical disease- or therapy-associated signs and symptoms (gastrointestinal symptoms, mental symptoms, dyspnoea, headache, tumour pain, cachexia, skin disorders, infections, and side effects associated with the antineoplastic therapy) in patients with breast cancer. Imbalances for causal effects (covariates) were adjusted for by means of the propensity score. Outcome analysis was performed by estimating the linear regression between change in symptom score and propensity score with all data and using this regression line to calculate the change in symptom score which would be expected for each patient. Tumour-associated events (recurrence, metastasis, and death) were evaluated in terms of the number of events observed and time to event. The safety of treatment with OE was analysed in terms of the number and severity of adverse events, their duration, treatment and outcome. *Results*: For all symptoms except tumour pain, the adjusted mean improvement in symptom scores was larger in the test group than in the control group. The adjusted difference was statistically significant for all symptoms, except tumour pain and infections. The results show that the typical disease- and therapy-associated signs and symptoms in patients on complementary therapy with OE during postoperative treatment were significantly less. For 75% of the test group and 55% of the control group the physician recorded "no signs and symptoms". A clear reduction in the side effects of radiotherapy and chemotherapy was documented in 74% of the test group and 55% of the control group. Analysis of survival, recurrence, and metastasis demonstrated a reduced number of events in the test group. There was evidence of a beneficial influence of OE on time to event, although the median observation time was too short in these breast cancer patients to draw definite conclusions. The safety component was judged in 98% of the test group and 76% of the control group as "very good" or "good". In the total sample of 2339 patients, the rate of OE-associated

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adverse reactions was 3.2%. All side effects were mild to moderate gastrointestinal symptoms. *Conclusion*: Complementary treatment of breast cancer patients with OE improves the quality of life by reducing signs and symptoms of the disease and the side effects of adjuvant antineoplastic therapies. This epidemiological retrolective cohort analysis provides evidence that the patients may also gain benefit by a prolongation of the time to event for cancer recurrence, metastasis and survival. OE was generally well tolerated.

Key words Retrolective cohort study · Complementary treatment · Breast cancer · Oral enzyme preparation · Symptoms · Events

Introduction

UICC stage I, II, and IIIA breast cancers generally require multimodal treatment consisting of surgery plus adjuvant radiotherapy or chemotherapy, or hormonal therapy. The objectives of these treatments include prolongation of survival, prevention of local recurrence or recurrence in regional lymph nodes, generation of prognostic information on the type and size of the tumour and on the status of the axillary lymph nodes, optimization of the aesthetic result, minimization of psychosocial effects and therapy-induced side effects, and optimization of the quality of life. In women with early stages of disease the tumour can be resected surgically, but they are at risk of developing local recurrence and metastases. It is during adjuvant therapy and thereafter that women often request other treatments to improve their quality of life and to prolong the success of their treatment [9, 10, 13, 14, 18, 24, 35].

Complementary therapeutic approaches have an important role to play, alongside the standard antineoplastic treatment programmes and include for example phytoextracts and organoextracts, antioxidant vitamins, trace elements, and oral enzyme (OE) preparations. While these complementary treatments are not an alternative to the established antineoplastic approaches, they may be valuable in the optimization of these therapies [2–5, 26].

OE preparations have long been available on the German market but their mechanism of action in complementary cancer therapy is not fully understood. There are a variety of mechanisms by which they are thought to contribute to antineoplastic efficacy. Orally administered proteases are known to bind irreversibly to antiproteinases such as α_2-macroglobulin and α_1-antitrypsin leading to synthesis of antiproteinases. Increased levels of antiproteinases inactivate other proteinases, e.g. cathepsins, which are thought to play a role in tumour development and metastasis. Cysteine proteinases of plant origin (papain) are known to influence the balance between proteinase and antiproteinase and as a consequence may also influence tumour metastasis [15, 17]. Furthermore, enzymes are known to interact with the cytokine network. The binding of proteinases to α_2-macroglobulins leads to the formation of α_2-macroglobulin-proteinase complexes with a high capacity for binding and clearing cytokines, e.g. IL-1β, IL-6, IFN-γ, and TGF-β. TGF-β promotes immunosuppression in the host and tumour immune escape thus modulating tumour growth [34]. Also enzymes reduce TGF-β overproduction at the levels of mRNA and protein synthesis [8, 22].

Enzymes also interact with adhesion molecules which play an important role in tumour development and metastasis. The modulation or downregulation of adhesion molecules by enzymes has been shown amongst others for B7-1, CD4, CD29, CD44, CD49, CD51, CD54, and CD58 which may contribute to their antitumour efficacy [27, 38]. Finally, enzymes influence the levels of antioxidant enzymes and reactive oxygen molecules. An increase in the synthesis of antioxidative protective mechanisms as shown by a small chronic oxidative stress has been shown in patients with burn injuries [23, 37]. Recently a novel role for extracellular proteases as inhibitors of intracellular signal transduction pathways has been described [25].

These results obtained in both experimental and preclinical settings support the role of enzymes as a potential candidate in rational complementary tumour therapy. However, convincing clinical evidence of their efficacy is still limited. The use of epidemiological methods in collecting and analysing existing data provides the means not only to evaluate the safety and efficacy of a particular treatment, but also to generate hypotheses for the development of well-designed prospective clinical trials. It is the goal of the scientific complementary oncology community to subject all cancer treatments to critical evaluation through appropriately designed and conducted clinical trials. This paper describes the use of today's methodology for epidemiological studies in assessing the efficacy of complementary OE medication in patients with breast cancer.

Methods

Study subjects

A total of 216 study centres were identified in Germany (hospitals, hospital units with beds at physician's disposal, specialist practices) and supplied data on 2339 patients with breast cancer of whom 1283 were receiving complementary treatment with OE (Wobe-Mugos E, MUCOS Pharma, Geretsried, Germany), and 1056 were not. The criteria for inclusion in the study cohort were: primary nonmetastasized breast cancer, age 18–80 years, treatment 1991 to 1997 with OE (test group) or without OE (control group) in addition to antineoplastic therapy (primary surgical treatment, radiation, adjuvant systemic hormonal or/and chemotherapy). Since patients could have received other complementary medications, e.g. physical therapy, phytoextracts or organic extracts, trace elements or vitamins, for the purpose of the analysis presented here, they were excluded if they received other complementary medications or another additive enzyme therapy, suffered a relapse or had developed metastases at the beginning of the postoperative treatment, or if a secondary malignancy was present.

Data collection

Prior to data collection the data elements required for the study were identified and defined in the trial protocol and a case report form. Data were retrieved by the investigators from the patients' medical records at the study centres and transferred to the standardized case report forms. Data collected included patients demographic details, characteristics of the tumour disease, treatments, signs, symptoms and side effects experienced by the patient, and the course of the disease. A clinical quality assurance audit was carried out by an independent institution which confirmed that the data were acceptable for the purpose of a clinical trial.

Study endpoints/statistical methods

The study design was a retrolective cohort analysis with parallel groups [11, 12, 19, 20, 29]. Design and conduct of the study were performed to current standards for prospective, controlled clinical trials [16, 36].

Assignment to OE (propensity score)

As the assignment to treatment with OE was not randomized, it may have depended on the characteristics of the patients or centres, or on additional treatments. These factors may also have influenced the treatment response. The responses had to be adjusted for these factors (covariates). The dependence of treatment assignment from patient and centre characteristics is described by the propensity score, i.e. the probability of treating a patient with OE as a function of these characteristics. The use of a propensity score for the adjustment of imbalances in observational studies for causal effects was introduced by Rosenbaum and Rubin, who showed that adjustment for the propensity score is sufficient to remove bias due to all observed covariates [7, 28, 30, 31, 33].

Outcome analysis

OE could reduce the typical disease-associated signs and symptoms in patients with breast cancer. The signs and symptoms were assessed based on the data collected from patients' records at the start and end of the period of postoperative treatment.

Signs and symptoms were allocated scores of 0 (no symptoms), 1 (mild) or 2 (severe). The following symptoms were recorded: gastrointestinal symptoms (nausea, vomiting, changes in appetite, stomach pain or stomach disorder), mental conditions (tiredness, depression, memory or concentration disorder, sleep disturbance, dizziness, irritability), dyspnoeic symptoms (dyspnoea at rest, dyspnoea during activity), headache, tumour pain, cachexia, skin disorders and infections. For a specific symptom a patient was included in the analysis if the symptom was present either at the beginning and/or the end of postoperative treatment, but only if an assessment was available for both time-points. The primary target criterion was the change in symptom score between the start and end of postoperative treatment.

In a first analysis the symptom scores were considered as quantitative variables and the distribution of changes was characterized by its mean. The analysis sought to determine whether this mean was greater in the test group than in the control group. As the assignment to OE differed between practitioners and specialists, the number of patients with complaints for these two specifications was separated. The difference in the mean changes between the test and control groups was tested using Student's *t*-test.

Success of therapy

In a second analysis, the therapy of a complaint was considered successful if the symptom was present at the beginning of postoperative treatment but absent at the end of treatment. A patient was included in this particular analysis if she presented with symptoms either at the beginning or the end of the postoperative treatment.

Events

Tumour events (recurrence, metastasis, death) were evaluated in terms of the number of events and time-to-event. The number of events was analysed in contingency tables using the χ^2-test and Fisher's exact test, and the odds-ratios at the 95% confidence interval were calculated. The time-to-event was calculated by the Kaplan-Meier method using the log-rank test for the difference between the treatment groups. The Cox proportional hazard regression method was used to adjust the results for all potential confounding criteria. The adjusted ratio with 95% confidence intervals was calculated.

Safety

Analysis of safety of the treatment with OE consisted of analysis of the number and severity of adverse events (AEs), the duration, treatment and the outcome of AEs. The comparison between the treatment groups was performed using contingency tables using the χ^2-test and the Fisher's exact test, respectively, and the odds ratios with their 95% confidence intervals were calculated.

Results

Characteristics of patients, centres and treatment

Data from the medical records of 822 women with primary nonmetastasized breast cancer were extracted at 128 centres (physicians) in Germany. The women underwent postoperative treatment during 1991 to 1997 with OE or without OE complementary to antineoplastic therapy (surgery, radiation, adjuvant chemotherapy, systemic hormonal therapy). The patients did not receive other complementary medications.

The primary aim of the study was to analyse the influence of complementary treatment with OE on typical signs and symptoms during primary antineoplastic therapy (radiation, adjuvant chemotherapy, systemic hormonal therapy) and during postoperative treatment. As this enzyme product has been on the market in its current composition since November 1991, data from patients with postoperative treatment before this date were excluded from the analysis (88 patients). In addition, the data from patients treated before surgery (additional 54 patients), or when the postoperative treatment was continued for less than 1 day (additional 31 patients) were excluded. In total, the data from 173 patients were excluded. The final analysis was performed on data from 649 patients, of whom 239 (37%) were treated with complementary OE (test group) and 410 (63%) without OE (control group).

Both groups were comparable in terms of age and Broca index. The mean age was 59 years in the test group and 60 years in the control group. The mean Broca index was 101% in the test group and 105% in the control group. The duration of postoperative treatment varied in the test group between 28 and 1882 days (median 485 days) and in the control group between 28 and

1948 days (median 213 days). The frequencies of primary surgery are shown in Table 1, those of postoperative TNM(G) classification in Table 2, and other postoperative tumour characteristics in Table 3. There were no clinically relevant differences between the test and control groups. The characteristics of the physicians (centres) are given in Table 4. There were considerable differences in characteristics between the groups: 64% of the physicians were more than 45 years of age in the test group compared to 37% in the control group; 65% of the patients in the test group and 21% in the control group were treated by general practitioners; 75% of test group and 53% of control group patients were outpatients. These data indicate that the prescription of OE was more likely among older physicians and general practitioners.

Since these inconsistencies could have biased the results an adjustment had to be made to provide equal conditions. Of the adjuvant therapies radiotherapy, chemotherapy and hormones were the most common. The frequencies are given in Table 5. Radiotherapy was used in 65% of the patients in the test group and in 72% in the control group. Chemotherapy was administered to 21% of patients in the test group and to 31% in the control group. The use of hormones was less frequent in the test group (39%) than in the control group (56%).

Table 1 Patient characteristics: frequency of primary surgery

Tumour surgery	Test group	Control group	Total
Not specified	2 (0.8%)	3 (0.7%)	5 (0.8%)
Tumorectomy	73 (30.5%)	182 (44.4%)	255 (39.3%)
Partial resection	51 (21.3%)	65 (15.9%)	116 (17.9%)
Ablation	61 (25.5%)	116 (28.3%)	177 (27.0%)
Mastectomy	52 (21.8%)	44 (10.7%)	96 (14.8%)
Total	239	410	649

Table 2 Patient characteristics: postoperative TNM(G) classification (*X* not clearly defined)

Classification	Test group	Control group	Total
T in situ	3 (1.3%)	5 (1.2%)	8 (1.3%)
T 1	122 (52.1%)	203 (50.4%)	325 (51.0%)
T 2	94 (40.2%)	165 (40.9%)	259 (40.7%)
T 3	13 (5.6%)	17 (4.2%)	30 (4.7%)
T 4	1 (0.4%)	12 (3.0%)	13 (2.0%)
T X	1 (0.4%)	1 (0.2%)	2 (0.3%)
Total	234	403	637
N 0	142 (60.9%)	247 (60.5%)	389 (60.7%)
N 1	81 (34.8%)	138 (33.8%)	219 (34.2%)
N 2	7 (3.0%)	18 (4.4%)	25 (3.9%)
N X	3 (1.3%)	5 (1.2%)	8 (1.2%)
Total	233	408	641
M 0	223 (95.7%)	374 (94.0%)	597 (94.6%)
M X	10 (4.3%)	24 (6.0%)	34 (5.4%)
Total	233	398	631
G 1	53 (24.8%)	39 (10.5%)	92 (15.7%)
G 2	106 (49.5%)	216 (57.9%)	322 (54.9%)
G 3	49 (22.9%)	99 (26.5%)	148 (25.2%)
G X	6 (2.8%)	19 (5.1%)	25 (4.3%)
Total	214	373	587

Other therapies (mainly physical therapy) were used in 12% of patients in the test group and 21% in the control group.

The use of the propensity score in managing influencing factors

The propensity score for an observational cohort study can be estimated by logistic regression of treatment assignment to the covariates of the study. To estimate the propensity score for assignment to OE the following covariates were used: patient's age, tumour stage (UICC), response to primary therapy, duration of postoperative treatment, use of adjuvant therapies during postoperative treatment (radiation therapy, chemotherapy, hormones, or physical therapy), physician's age, physician's specialization, physician's place of practice. For those case for which these covariates were missing, the propensity score was estimated with all the nonmissing covariates [31, 32].

The following covariates showed a significant influence on the decision to treat with OE: patient's age, therapy with hormones, physician's specialization, and physician's place of practice. The physician's speciality was the greatest influence. The predictive power of the estimated propensity score was rather high. Using as the cut-off point a probability of 0.5 (i.e. predicting assignment to OE for the given covariates of a patient if the propensity score was greater than 0.5), 81% of the actual treatment assignment could be predicted correctly.

Outcome analysis

The primary aim of the study was to determine whether complementary treatment of patients with breast cancer with OE during the postoperative period could reduce disease-associated signs and symptoms or side effects of the antineoplastic therapies (radiation, chemotherapy, hormonal therapy). For a specific symptom a patient was included in the analysis if the symptom was present in her medical record at the beginning and/or the end of postoperative treatment. Patients not showing a symptom at the beginning and/or the end of postoperative treatment were excluded from that particular analysis. The primary target criterion was the change in symptom scores from the beginning to the end of postoperative treatment.

Change in symptom scores

In one analysis the symptom scores were considered as quantitative variables and the distribution of changes was characterized by its mean. The analysis sought to determine whether the mean symptom score change was larger (i.e. more beneficial) in the test group than in the control group.

For unbiased results, the changes in symptom scores were adjusted for the value of the propensity score. This

Table 3 Patient characteristics: postoperative tumour characteristics

	Test group	Control group	Total
Postoperative residual tumour			
None	179 (94.2%)	308 (95.4%)	487 (94.9%)
Microscopic	9 (4.7%)	12 (3.7%)	21 (4.1%)
Macroscopic	2 (1.1%)	3 (0.9%)	5 (1.0%)
Total	190	323	513
Tumour location			
Left	124 (51.9%)	197 (48.6%)	321 (49.8%)
Right	113 (47.3%)	202 (49.9%)	315 (48.9%)
Both sides	2 (0.8%)	6 (1.5%)	8 (1.2%)
Total	239	405	644
Tumour type			
Unknown	13 (6.3%)	13 (3.7%)	26 (4.7%)
Solitary	161 (77.4%)	304 (87.6%)	465 (83.8%)
Multiple	34 (16.3%)	28 (8.1%)	62 (11.2%)
Disseminated		2 (0.6%)	2 (0.4%)
Total	208	347	555
UICC stage			
0 or I	81 (35.4%)	148 (37.9%)	229 (36.9%)
IIa	92 (40.2%)	129 (33.0%)	221 (35.6%)
IIb	43 (18.8%)	77 (19.7%)	120 (19.4%)
IIIa or higher	13 (5.7%)	37 (9.5%)	50 (8.1%)
Total	229	391	620
Response			
Complete remission	224 (94.9%)	352 (94.9%)	576 (94.9%)
Partial remission	11 (4.7%)	16 (4.3%)	27 (4.4%)
Minimal recovery	1 (0.4%)	3 (0.8%)	4 (0.7%)
Total	236	371	607

Table 4 Description of study centres for the total study sample

	Test group	Control group	Total
Doctor's gender			
Male	178 (78.1%)	366 (90.1%)	544 (85.8%)
Female	50 (21.9%)	40 (9.9%)	90 (14.2%)
Total	228	406	634
Doctor's age			
≤ 45 years	65 (36.3%)	245 (62.7%)	310 (54.4%)
>45 years	114 (63.7%)	146 (37.3%)	260 (45.6%)
Total	179	391	570
Physician's specialization			
General practitioner	155 (64.9%)	87 (21.2%)	242 (37.3%)
Internal specialist	11 (4.6%)	40 (9.8%)	51 (7.9%)
Gynaecologist	20 (8.4%)	47 (11.5%)	67 (10.3%)
Oncologist	1 (0.4%)	151 (36.8%)	152 (23.4%)
Radiologist	49 (20.5%)	85 (20.7%)	134 (20.6%)
Surgeon	3 (1.3%)		3 (0.5%)
Total	239	410	649
Physician's place of practice			
Private office	179 (74.9%)	219 (53.4%)	398 (61.3%)
Hospital	1 (0.4%)	151 (36.8%)	152 (23.4%)
Hospital aftercare	3 (1.3%)	21 (5.1%)	24 (3.7%)
Oncological office	46 (19.2%)	9 (2.2%)	55 (8.5%)
Office and hospital	10 (4.2%)	10 (2.4%)	20 (3.1%)
Total	239	410	649

was done by estimating the linear regression between the change in symptom score and propensity score with all data and calculating with this regression line for each patient the change in symptom score which would be expected if the propensity score were set to the general mean of 0.387. For these adjusted changes the means

were calculated within each therapy group and the difference between the groups was tested using the *F*-test.

Table 6 shows for each symptom investigated and for each patient group the mean scores at the beginning and the end of postoperative treatment, the adjusted mean changes, the difference in adjusted mean changes between the test and control groups, and the *P*-value of the *F*-test.

For all symptoms, except tumour pain, the adjusted mean change in symptom scores was larger in the test group than in the control group. The adjusted difference was statistically significant for all symptoms, except tumour pain and infections. Therefore, complementary therapy with OE led to a significant reduction in complaints during the postoperative treatment, provided the same baseline and treatment conditions for all patients (except treatment with or without OE) are given.

Table 5 Distribution of primary antineoplastic therapies

	Test group	Control group	Total
Radiotherapy			
No	84 (35.1%)	113 (27.6%)	197 (30.4%)
Yes	155 (64.9%)	297 (72.4%)	452 (69.6%)
Total	239	410	649
Chemotherapy			
No	188 (78.7%)	284 (69.3%)	472 (72.7%)
Yes	51 (21.3%)	126 (30.7%)	177 (27.3%)
Total	239	410	649
Hormone therapy			
No	145 (60.7%)	180 (43.9%)	325 (50.1%)
Yes	94 (39.3%)	230 (56.1%)	324 (49.9%)
Total	239	410	649
Other therapies (supportive care)			
No	211 (88.3%)	325 (79.3%)	536 (82.6%)
Yes	28 (11.7%)	85 (20.7%)	113 (17.4%)
Total	239	410	649

Success of therapy

Table 7 shows the effect of adjustment for the propensity score (observed and adjusted odds ratio with 95% confidence interval for the adjusted odds ratio). Adjustment for propensity score was performed with logistic regression.

The adjusted odds ratios were significantly larger than 1 for the symptoms gastrointestinal complaints, cachexia and skin reactions. For dyspnoea the *P*-value was nearly at the 0.05 level ($P = 0.056$). The optimization of the OE therapy was less pronounced than the improvement by reduction in the symptom score. Nevertheless, for all symptoms the adjusted success was greater for the test group than for the control group.

Judgement of efficacy by the physician

For each patient the physician gave a judgement about efficacy, safety, and influence on the reduction of side effects of chemotherapy or radiotherapy. The results are summarized in Table 8. For 75% of the test group and 55% of the control group the physician rated "no signs and symptoms". The safety was judged in 98% of the test group and 76% of the control group as "very good" or "good". A clear reduction in the side effects of radiotherapy or chemotherapy was given for 74% of the test group and 55% of the control group. Side effects were reported for 69 (29.7%) of the patients in the test group and 254 (62.3%) of the patients in the control group. None of these side effects was related to the complementary therapy with OE.

Table 6 Mean values of observed symptom scores at beginning and end of aftercare and the observed changes and adjusted changes adjusted for propensity score

Signs and symptoms	Group	*n*	Observed mean score			Adjusted for propensity score		
			Beginning	End	Change	Change	Difference	*P*-value
Gastrointestinal	Test	140	0.38	0.17	0.21	0.27	0.16	0.005
	Control	203	0.39	0.24	0.15	0.11		
Mental	Test	201	0.55	0.32	0.23	0.26	0.14	0.005
	Control	322	0.50	0.35	0.15	0.12		
Dyspnoeic	Test	52	0.68	0.57	0.12	0.20	0.42	0.012
	Control	60	0.55	0.69	–0.14	–0.22		
Headache	Test	50	0.94	0.50	0.44	0.44	0.36	0.036
	Control	85	0.81	0.73	0.08	0.08		
Tumour pain	Test	51	1.04	0.45	0.59	0.48	–0.20	0.272
	Control	47	1.04	0.47	0.57	0.68		
Cachexia	Test	23	1.04	0.48	0.56	0.66	1.16	0.002
	Control	14	0.93	1.29	–0.36	–0.50		
Skin reactions	Test	85	0.75	0.64	0.12	0.65	0.50	0.006
	Control	227	0.80	0.44	0.36	0.15		
Infections	Test	52	1.19	0.60	0.59	0.50	0.26	0.125
	Control	70	1.00	0.84	0.16	0.24		

Table 7 Treatment success adjusted for propensity score

Signs and symptoms	Group	*n*	Success		Odds ratio		95% CI	*P*-value
			n	%	Crude	Adjusted		
Gastrointestinal	Test	140	59	42	1.270	1.843	1.022–3.321	0.042
	Control	203	74	36				
Mental	Test	201	49	24	0.992	1.113	0.636–1.948	0.707
	Control	322	79	24				
Dyspnoeic	Test	52	16	31	2.222	3.105	0.972–9.918	0.056
	Control	60	10	17				
Headache	Test	50	25	50	2.400	1.568	0.652–3.773	0.315
	Control	85	25	29				
Tumour pain	Test	51	33	65	1.244	0.705	0.266–1.871	0.483
	Control	47	28	60				
Cachexia	Test	23	15	65	24.375	133.95	3.695–4855	0.008
	Control	14	1	7				
Skin reactions	Test	85	32	38	0.397	3.028	1.371–6.685	0.006
	Control	227	137	60				
Infections	Test	52	25	48	2.887	1.318	0.473–3.672	0.597
	Control	70	17	24				

Table 8 Physician's judgement on efficacy, safety, and on reduction of side effects of radiotherapy or chemotherapy

	Test group	Control group	Total
Efficacy of therapy			
No complaints	177 (75.0%)	222 (55.4%)	399 (62.6%)
Clear recovery	38 (16.1%)	95 (23.7%)	133 (20.9%)
Moderate recovery	5 (2.1%)	61 (15.2%)	66 (10.4%)
Unchanged	13 (5.5%)	14 (3.5%)	27 (4.2%)
Worsened	3 (1.3%)	9 (2.2%)	12 (1.9%)
Total	236	401	637
Reduction of side effects of radio-, chemo, hormone therapy			
Clearly reduced	133 (74.3%)	168 (54.5%)	301 (61.8%)
Moderately reduced	22 (12.3%)	82 (26.6%)	104 (21.4%)
No influence	24 (13.4%)	51 (16.6%)	75 (15.4%)
Increased		7 (2.3%)	7 (1.4%)
Total	179	308	487
Safety of therapy			
Very good	162 (68.4%)	158 (39.7%)	320 (50.4%)
Good	71 (30.0%)	145 (36.4%)	216 (34.0%)
Average	2 (0.8%)	83 (20.9%)	85 (13.4%)
Unsatisfactory	1 (0.4%)	10 (2.5%)	11 (1.7%)
Poor	1 (0.4%)	2 (0.5%)	3 (0.5%)
Total	237	398	635
Adverse drug reactions			
Yes	69 (29.7%)	254 (62.3%)	323 (50.5%)
No	163 (70.3%)	154 (37.7%)	317 (49.5%)
Total	232	408	640

Survival, cancer recurrence, and metastases

In the test group 3 patients (1.26%) died from tumour-related disease during the postoperative period, compared to 11 patients (2.68%) in the control group. The mean survival time from initiation of postoperative treatment was 1840 days (5.04 years) in the test group, and 1820 days (4.99 years) in the control group ($P = 0.0787$, log rank test). The survival details are shown in Fig. 1.

Cancer recurrence was observed in 6 patients (2.50%) in the test group and 26 patients (6.34%) in the control group. The mean time to recurrence (from initiation of postoperative treatment) was 1818 days (4.98 years) in the test group and 1702 days (4.66 years) in the control group ($P = 0.0055$). The survival details for cancer recurrence are shown in Fig. 2.

Metastases were observed in 12 patients (5.04%) in the test group and 31 patients (7.58%) in the control group. The mean time from the start of postoperative treatment to metastasis was 1738 days (4.76 years) in the test group and 1665 days (4.56 years) in the control group ($P = 0.0475$). The survival details are shown in Fig. 3.

Safety and dosage of OE

Amongst the total sample of 2339 patients, the rate for OE-associated adverse reactions was 3.2%. All side effects were mild to moderate gastrointestinal symptoms of which none required special measures, e.g. dose reduction, discontinuation of therapy with OE, or symptomatic treatment. Long-term treatment with OE was found to be more efficient than interval or acute therapy. The dose used most frequently was the recommended dosage of two tablets three times daily. Patients were also treated with higher doses (up to 40 tablets per day) which were tolerated without problems. Measurable effects of the therapy such as alleviation of the signs and symptoms of disease and a reduction in the adverse reactions to radio- and chemotherapy were observed within weeks (data not shown).

Discussion

This observational study was designed to investigate the benefits to breast cancer patients of receiving OE therapy after primary surgery as complementary therapy during or after adjuvant radiotherapy, chemotherapy, or hormonal therapy. The study type chosen for this investigation was a multicentric, retrolective cohort analysis with parallel groups, in which patients receiving OE were compared with patients not receiving OE.

From preliminary results of earlier studies the primary endpoint was defined as a reduced incidence of

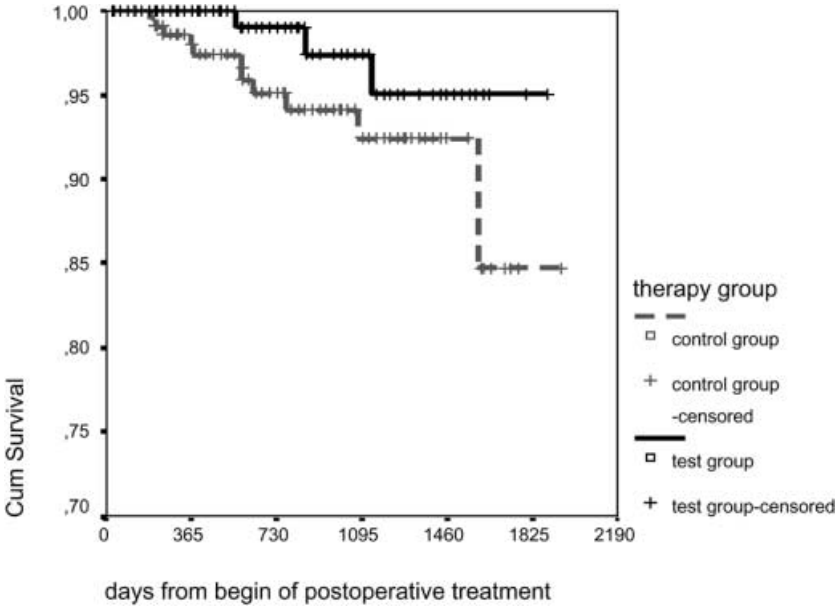

Fig. 1 Estimated survival curves for OE-treated patients and for control group patients

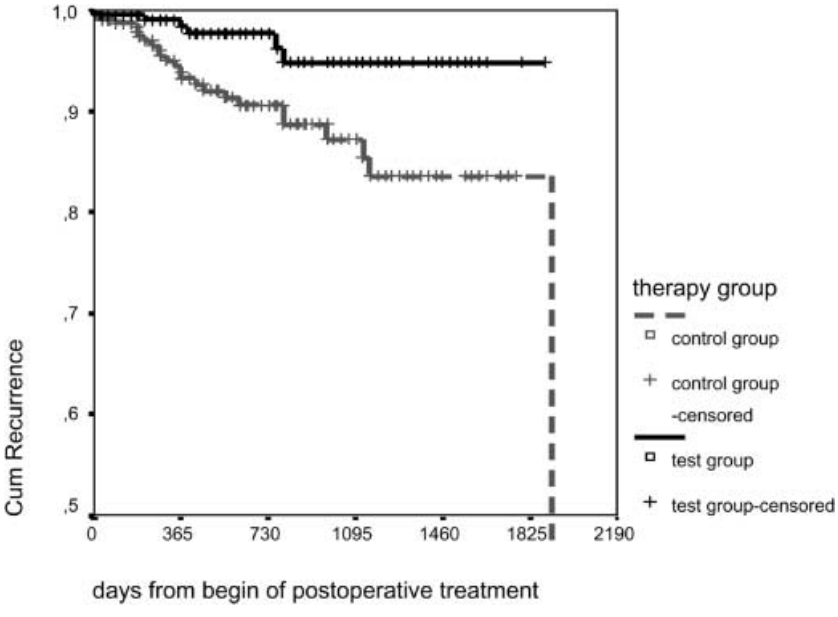

Fig. 2 Estimated survival function for cancer recurrence

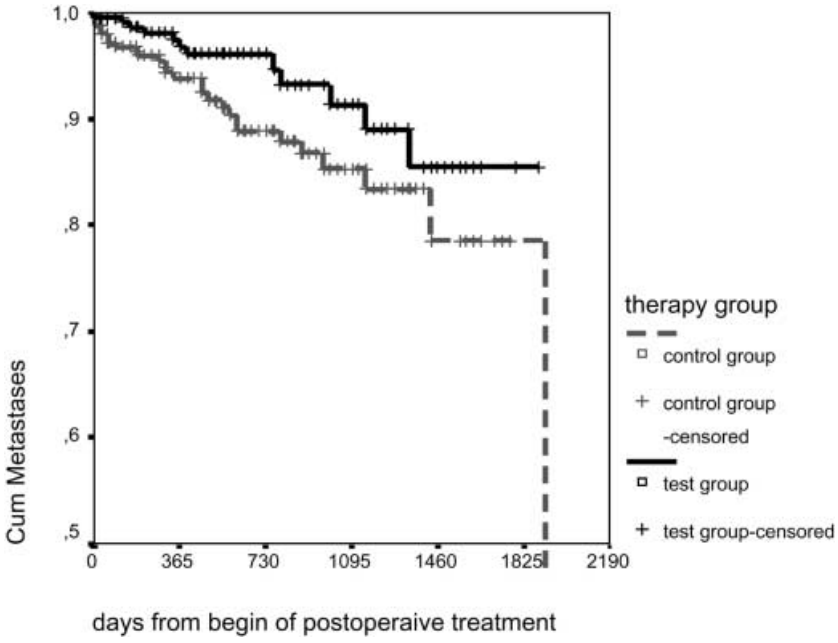

Fig. 3 Estimated survival function for occurrence of new metastases

both breast cancer-associated symptoms and side effects of the antineoplastic therapy [21]. The question as to whether OE therapy not only improved the quality of life but also influenced the time to occurrence of an event (recurrence, metastasis, death) was also investigated.

The present data collected on 2339 patients included more than 90 different complementary treatment schemes including physical therapy, phytoextracts or organic extracts, trace elements or vitamins combined with OE. In the absence of a rationale in most cases, it is of interest to gain more information on the efficacy of individual drugs so as to eventually develop recommendations as to which drugs should be used and how they should be used. The analysis of the large body of data by observational studies is a sensitive and valid approach to achieving this goal. It has been shown recently that the results of well-designed observational studies do not indicate either consistently greater magnitudes of treatment effects and are not qualitatively different from those of randomized, controlled trials [1, 6]. Studies such as these can be used to generate hypotheses for the development of controlled prospective randomized clinical trials.

In this study only patients who did not receive other complementary drugs (control group) except for OE (test group) were selected. The results presented here show that complementary therapy with OE was statistically significantly superior to the control therapy in reducing gastrointestinal symptoms, mental disorders, dyspnoeic symptoms, headache, skin reactions, and especially cachexia. No significant effects on tumour pain and infections were observed. The results suggest that the intake of OE stabilized and improved the condition of the patient through its influence on the symptoms caused by the illness and by the antineoplastic therapy. Additionally, the frequency and severity of the adverse events caused by radiotherapy and chemotherapy were reduced. In addition, OE had an influence on tumour events. The recurrence- and metastasis-free survival as well as the overall survival time were prolonged in the test group. These results, however, have to be verified in a controlled, prospective randomized study since the observation time (10 months) was short. Therefore, the results presented here can only be regarded as a trend. Follow-up of the study cohort will result in the necessary observation times of several years, thus allowing for more valid conclusions. As the tolerability of the complementary treatment with OE was excellent and only a low rate of mostly mild side effects were recorded, treatment with OE can be regarded as being safe.

Due to the side effects of standard antineoplastic treatments especially in the palliative setting of breast cancer therapy, an additional treatment to improve the quality of life is a beneficial option for the patients. The results presented here suggest that treatment with OE could also lead to an improvement in patient survival. This has to be confirmed in future clinical trials. Therefore, OE is a promising complementary therapy option for the treatment of breast cancer but it has to be verified in prospective randomized trials.

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