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CLINICAL TRIAL

Prophylactic acupuncture treatment during chemotherapy with breast cancer: a randomized pragmatic trial with a retrospective nested qualitative study

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Abstract

Purpose This study investigated the effect of additional prophylactic acupuncture during chemotherapy on quality of life and side effects compared to standard treatment alone in breast cancer patients.

Methods In a pragmatic trial, newly diagnosed breast cancer patients were randomized to additional acupuncture treatments over 6 months or standard care alone (control group). The primary outcome was the disease-specific quality of life (FACT-B). Twenty qualitative semi-structured interviews were conducted with ten patients from each group regarding their subjective experiences.

Results A total of 150 women (mean age 51.0 (SD 10.0) years) were randomized. For the primary endpoint, FACT-B total score after 6 months, no statistically significant difference was found between groups (acupuncture: 103.5 (95%, CI 88.8 to 107.2); control (101.4 (− 97.5 to 105.4); difference 2.0 (− 3.4 to 7.5) $p = 0.458$)). Qualitative content analyses showed that patients in the acupuncture group described positive effects on psychological and physical well-being. For both patient groups, coping strategies were more important than reducing side effects.

Conclusions Breast cancer patients receiving prophylactic acupuncture during chemotherapy did not show better quality of life in the questionnaires in contrast to the reported positive effects in the qualitative interviews. Coping strategies for cancer appear to be important.

Trial registration clinicaltrials.gov; NCT01727362. Prospectively registered 11 July 2012; https://clinicaltrials.gov/ct2/show/NCT01727362. The manuscript adheres to CONSORT guidelines.

Keywords Acupuncture · Breast cancer · Quality of life · Complementary medicine · Pragmatic trial · Comparative effectiveness research

Background

Breast cancer (BC) is the most common cancer in women. Cancer treatments including surgery, chemotherapy, radiotherapy, and endocrine therapy have developed substantially over the last two decades [1]. Although treatment plans are less intense than in earlier periods [1] and patients experience fewer side effects, breast cancer patients are high users of complementary and integrative medicine (CIM) with the aim to improve their quality of life before, during and after primary cancer treatment [2–5]. Most breast cancer patients have a strong wish for more integration of CIM into cancer care [6]. A trial from North Italy showed that breast cancer patients who received individualized multicomponent CIM

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interventions in addition to cancer care had a better quality of life [7].

In several clinical studies of heterogeneous trial methodologies and different sample sizes in cancer patients, acupuncture demonstrated beneficial effects in reducing side effects, including nausea and vomiting [8, 9], fatigue [10, 11], pain [12, 13] vasomotor symptoms, and hot flashes [14–16]. In contrast, acupuncture was not effective in reducing breast cancer-related lymphedema in a randomized controlled trial [17]. In a recently published trial, acupuncture showed positive effects in improving joint pain related to aromatase inhibitor among woman with early-stage breast cancer [18]. Furthermore, acupuncture was positively evaluated in review articles on cancer patients in general [19–21] and in BC patients in particular [22–24]. The results were included in several German and international guidelines [24, 25].

The aim of this study was to investigate the effectiveness of additional prophylactic acupuncture treatment during chemotherapy on the quality of life and side effects of chemotherapy compared to standard treatment alone in breast cancer patients.

Methods

Design

This randomized pragmatic trial took place between October 2012 and April 2015 at the breast cancer center of the Jerusalem Hospital in Hamburg, Germany. Women with breast cancer were randomized to 6 months of standard treatment and additional acupuncture or standard therapy alone (control group). Outcomes were assessed at baseline and after 3 and 6 months. Randomization was stratified by chemotherapy regimen and in blocks of variable length to balance groups for chemotherapy treatment plans. Randomization lists were generated with SAS Version 9.4 (SAS Institute, Cary, NC, USA) by a statistician not further involved in the study, using a 1:1 allocation ratio. To ensure allocation concealment, the randomization list was embedded in an MS ACCESS secure database that could not be accessed by study personnel. Before randomizing a patient, the patient identification data had to be entered and could not be changed or deleted after randomization. The trial statistician and data entry personnel were blinded to the treatment assignment throughout the study.

The study followed the Declaration of Helsinki and Good Clinical Practice guidelines and was registered under NCT01727362 (clinicaltrials.gov). All study participants provided written, informed consent and were not reimbursed for participating.

Patients

All patients were recruited at the breast cancer center of the Jerusalem Hospital and were screened first by the study nurses and then by a gynecologist. Female patients were included if they were at least 18 years of age with newly diagnosed and not yet treated chemotherapy asymptomatic breast cancer (histologic invasive ductal and lobular carcinoma, hormone sensitive and non-sensitive, HER2-receptor positive and negative) without distant metastasis, and with chemotherapy regimens (Table 2) planned.

Exclusion criteria were non-regional metastasis, treatment with anticoagulants or a bleeding disorder, and serious psychiatric or other disease that did not allow regular study participation.

Interventions

Acupuncture group

An experienced Chinese medicine practitioner with more than 30 years of practice in Chinese-style acupuncture and more than 20 years in treating cancer patients provided the acupuncture treatment. Patients in the acupuncture group received semi-standardized body acupuncture treatment following the clinical status of patients and a Chinese medicine pulse and tongue diagnosis. In case of side effects, predefined acupuncture points were included in the treatment: nausea, vomiting and gastrointestinal symptoms—PC6, ST 36, ST 44, CV10, and CV12; polyneuropathy—ST36, ST42, LI11, LI10, Extra Points Baxie and Bafeng; articular and muscle pain—LI10, LI11, ST36, GB 34, GB 39; cancer-related fatigue—GV20, ST36, LI 10, CV 4 and 6; and depression and anxiety—PC6, HE7, HE 6, and KID4. The number of acupuncture treatments and additional points were determined by the acupuncturist following the individual patient symptoms and the Chinese pattern diagnosis. Only needle acupuncture with disposable one-time needles was allowed. Neither the needle technique nor needle retention time was predefined, as was the case for de qi sensation, needle stimulation and depth of insertion. Forms of acupuncture treatment other than body acupuncture (e.g., moxibustion, laser acupuncture, electro-acupuncture), as well as other CIM treatments, were not permitted [26].

Control group

The control group was asked not to use any kind of acupuncture during the study period of 6 months after

randomization. As in the acupuncture group, no other CIM treatments were permitted.

Cancer treatment

Patients in both groups received one of the following chemotherapy treatment plans: FEC, FEC/DOC, EC/DOC, ECD, ECP, EC, or ECT and supportive conventional treatments as needed, according to current guidelines [27].

Outcome measurements

The primary outcome was the disease-specific quality of life (QoL) measured by the FACT-B total score [28] after 6 months (values of 0 to 144, with higher values indicating higher QoL). Secondary outcomes included the complaint-specific FACIT-fatigue questionnaire that included 13 questions regarding tiredness and fatigue symptoms [29], and the FACT-GOG-NTX to document neurotoxicity symptoms, classified as sensory, motoric and auditory changes [30] measured by 11 items on a 5-point Likert scale (0 = none; 4 = much); generic health-related quality of life was measured by the Short-Form (SF)-12 questionnaire [31, 32]. Further secondary outcome parameters included patient satisfaction with acupuncture treatment (very efficient/beneficial, efficient/beneficial, somewhat, or non-efficient/beneficial). Primary and secondary outcome parameters were evaluated using paper questionnaires.

Adverse effects (AEs) of the chemotherapy were documented in the hospital discharge letter for all available patients and subsequently transferred to the case report form. In addition, in the patient's health record, AEs of acupuncture were documented by the acupuncturist within the treatment documentation for the acupuncture group. All adverse effects of chemotherapy were classified by the Common Terminology Criteria for Adverse Events (CTCAE), NIH, Division of Cancer Treatment & Diagnosis [33].

Statistics

For the sample size calculation (using nQuery Advisor 6.02), we assumed a difference between the treatment groups of 10 points on the FACT-B total score (common standard deviation 20), corresponding to a moderate effect size of 0.5. Based on a two-sided *t* test with a significance level of 0.05 and power of 80%, 64 patients per group were needed. Assuming an approximate drop-out rate of 20%, we sought to enroll 150 patients.

Data analyses (performed with SAS for Windows, Version 9.4 (SAS Institute, Cary, NC, USA)) followed a predefined statistical analysis plan (SAP).

The primary analysis of the primary endpoint (FACT-B score after 6 months) was performed by an analysis of covariance (ANCOVA) with the treatment group (fixed effect) and the FACT-B baseline score as the covariate. The results for the treatment effect were presented as adjusted means per treatment group and group differences, with 95% confidence intervals and *p*-value (two-sided). All patients who provided data at baseline and 6 months for the primary outcome were included in the primary analyses, according to their treatment group. All further analyses (secondary outcomes, subgroups, sensitivity analyses) were performed on the patient population with available data and were considered exploratory.

Sensitivity analyses for the primary endpoint were based on the same ANCOVA model and included the following: (a) multiple imputation of missing values at 6 months with regression-based methods, (b) multiple imputation of missing values at baseline, (c) per-protocol population (excluding patients with non-invasive ductal carcinoma, receiving another chemotherapy regime as stratified in the randomization process, with distant metastasis, receiving fewer than 6 acupuncture sessions, receiving acupuncture in the first 6 months in the control group), (d) adjustment for strata and chemotherapy treatment regimes, and (e) a longitudinal model for the primary endpoint including 3- and 6-month data. Subgroup analyses for the primary endpoint were performed for chemotherapy regimens, menopausal status and severity of cancer-related fatigue at baseline by including the respective subgroup variable and interaction term in the original ANCOVA model.

For continuous secondary endpoints, ANCOVA adjusting for baseline values was employed. For binary outcomes (e.g., the proportion of responders, defined as patients who had at least 7-point improvements in the FACT Breast B scores), regression models adjusted for baseline values were used. Adverse events of acupuncture were described descriptively with frequency and percentage.

Nested qualitative study

A total of 20 semi-structured telephone interviews were conducted in a nested retrospective qualitative study. From each treatment group, five responders and five non-responders (defined by the primary outcome) were randomly selected. Randomization followed the chemotherapy regime in subsequent order, including patients with filled FACT-B questionnaires at baseline, after 3 and 6 months. For the acupuncture group, the assessment of the effectiveness of and satisfaction with acupuncture and having received at least 6 acupuncture treatments were parts of the randomization criteria.

The interviews were digitally recorded, pseudonymized, transcribed and then deductively and inductively analyzed according to Qualitative Content Analysis using the software MAXQDA® [34]. Main topics of the interview guideline in both groups were as follows: well-being and side effects

during chemotherapy, effects on everyday life and ways of dealing with the cancer disease and coping strategies. In the acupuncture group, the subjective experience of the acupuncture treatment and its perceived effects were part of the interview.

Results

A total of 362 breast cancer patients were screened for eligibility and 150 patients were randomized ($n=75$ acupuncture, $n=75$ control group) (Fig. 1).

Overall, baseline characteristics were comparable between both groups (Table 1). Patients were, on average, 51 (10 SD) years of age with a mean Body Mass Index of 25 (5 SD) with significant differences in school education. A total of 66% of the women were pre- or pre/perimenopausal. Regarding their breast cancer, 99% of patients had invasive ductal carcinoma and 56 (37.3%) had some form of lymph node metastasis (N1–N3) (Table 2). Most patients received as chemotherapy ECP (35.3%), EC/DOC (21.3%), FEC (20%), or FEC/DOC (17.3%). There were no significant differences between the groups regarding their expectation of an acupuncture treatment outcome at baseline. In the acupuncture group, the number of acupuncture sessions ranged between 1 and 22 [the average number of acupuncture sessions was 10.7 (4.8 SD)]. Furthermore, 26 (35.6%) patients underwent more than 12 sessions, 37 (50.7%) patients had between 6 and 12 sessions, and 10 (13.7%) underwent fewer than 6 sessions.

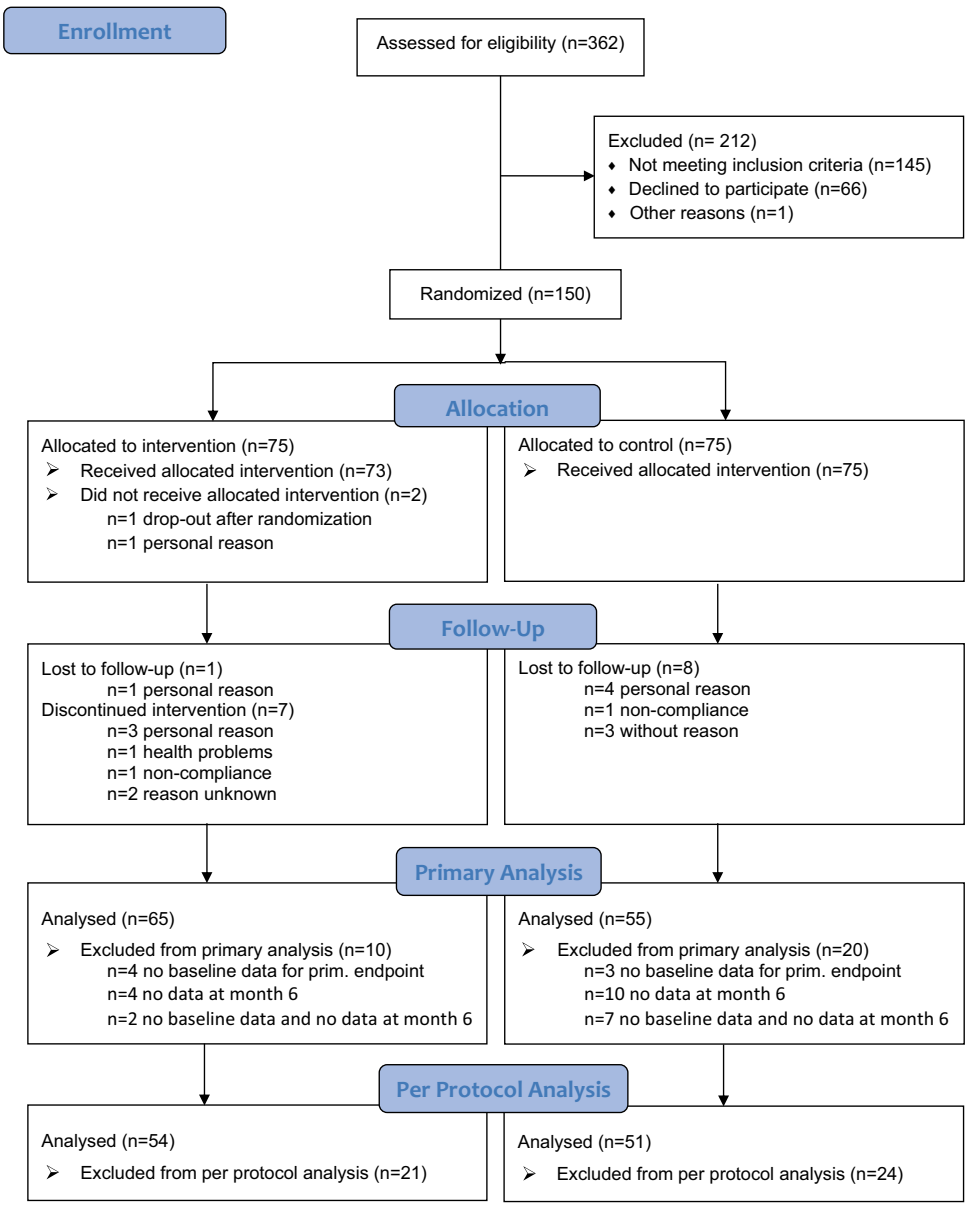

Fig. 1 Study—flowchart

Table 1 Baseline characteristics

Characteristics	Total $n=150$ Mean ± SD/ n (%)	Acupuncture $n=75$ Mean ± SD/ n (%)	Control $n=75$ Mean ± SD/ n (%)
Age (years)	51.0 ± 10.0	51.4 ± 10.4	50.6 ± 9.5
Body mass index	25.1 ± 5.1	25.9 ± 5.5	24.4 ± 4.5
Education			
Abitur (German University entrance qualification)	69 (48.9)	26 (35.1)	43 (64.2)
Menopause			
Pre-/perimenopausal	99 (66.4)	47 (62.7)	52 (70.3)
Postmenopausal	50 (33.6)	28 (37.3)	22 (29.7)
FACT-B total score, score range 0–144[b]	106.1 ± 18.5	105.6 ± 14.7	106.7 ± 21.9
FACT-B subscales			
Physical well-being subscale, score range 0–28[b]	22.4 ± 5.4	22.0 ± 5.2	22.8 ± 5.5
Social/family well-being subscale, score range 0–28[b]	24.3 ± 4.0	24.8 ± 2.9	23.7 ± 4.9
Emotional well-being subscale, score range 0–24[b]	16.9 ± 4.5	16.5 ± 4.4	17.4 ± 4.6
Functional well-being subscale, score range 0–28[b]	17.4 ± 5.5	16.9 ± 4.6	18.0 ± 6.4
Breast cancer subscale, score range 0–36[b]	24.8 ± 5.3	24.9 ± 4.5	24.7 ± 6.1
FACT-B single items			
Pain[d]	0.9 ± 1.0	0.9 ± 1.0	0.8 ± 1.0
Sleep[e]	2.4 ± 1.1	2.3 ± 1.0	2.6 ± 1.2
Nausea[d]	0.3 ± 0.7	0.4 ± 0.8	0.2 ± 0.6
FACT/GOG-NTX neurotoxicity, subscale, score range 0–44[c]	41.3 ± 3.1	41.3 ± 2.4	41.3 ± 3.7
FACIT-fatigue subscale, score range 0–52[b]	38.9 ± 10.4	38.6 ± 9.0	39.3 ± 11.9
Quality of life (SF-12)			
Mental component summary, score range 0–100[a]	47.7 ± 10.5	48.1 ± 9.7	47.3 ± 11.4
Physical component summary, score range 0–100[a]	44.1 ± 8.9	43.2 ± 8.4	45.0 ± 9.4

Values are absolute number (n) und percentage (%) or mean and standard deviation (SD)

FACT Functional Assessment of Cancer Therapy, *FACT-B* Functional Assessment of Cancer Therapy-Breast, *FACIT* Functional Assessment of Chronic Illness Therapy

[a]Higher values indicate better Qol

[b]The higher the score the better the Qol

[c]Higher scores indicates better Qol/less neuropathy

[d]High score indicates worse feeling

[e]High score indicates good feeling

After 6 months, the mean FACT-B total score (primary endpoint) was 103.5 (95% CI 99.8 to 107.2) in the acupuncture group and 101.4 (97.5 to 105.4) in the control group (difference 2.0, −3.4 to 7.5, $p=0.458$) (Table 3, Fig. 2). Findings were similar for the sensitivity analysis (Table 3). Findings were also similar using longitudinal analysis with all available data and when performing the other sensitivity analyses described above. Subgroup analyses showed no relevant differences with respect to treatment effect within the respective subgroups.

The proportion of treatment responders (defined as changes in FACT-B score of 7 points after 6 months versus baseline value) was 33.9% in the acupuncture group and 18.2% in the control group (odds ratio 2.2, $p=0.08$).

There were no significant differences between groups after 3 months with respect to FACT-B scores or any of the subscales (Table 3). This was similar for other secondary outcomes including fatigue (FACIT), chemotherapy treatment side effects (FACT-GOG-NTX) and general health-related quality of life (SF-12).

By contrast, most patients (91%) in the acupuncture group were very satisfied (75%) or satisfied (16%) with the study intervention, and most patients stated that the acupuncture was very effective (65%) or effective (28%) after 6 months.

In the hospital discharge letters, a total of 1188 AEs were documented as consequences of chemotherapy (Table 4). Most of these AEs belonged to the spectrum of gastrointestinal disorders (36%) and general disorders (25%). The mean number of AEs per patient was 8.0 (3.2 SD): acupuncture group 8.0 (3.1) and control group 8.2 (3.4). There were three serious AEs among three patients due to chemotherapy. Most AEs due to acupuncture (44 in

Table 2 Baseline:breast cancer—medical history

	Total $n=150$ n (%)	Acupuncture $n=75$ n (%)	Control $n=75$ n (%)
Primary tumor			
Breast cancer type			
Invasive ductal carcinoma	145 (98.64)	73 (98.65)	72 (98.63)
Invasive lobular carcinoma	1 (0.68)	0	1 (1.37)
Inflammatory breast cancer	0	0	0
LCIS/DCIS (carcinoma in situ)	0	0	0
TNM-staging			
T2	76 (51.70)	34 (45.95)	42 (57.53)
T1	68 (46.26)	38 (51.35)	30 (41.10)
T3	2 (1.36)	2 (2.70)	0
T4	1 (0.68)	0	1 (1.37)
N0	89 (61.38)	45 (61.64)	44 (61.11)
N1	51 (35.17)	25 (34.25)	26 (36.11)
N2	4 (2.76)	2 (2.74)	2 (2.78)
N3	1 (0.69)	1 (1.37)	0
M0	139 (100)	70 (100)	69 (100)
M1	0	0	0
Tumor grading			
G3	87 (60.00)	44 (60.27)	43 (59.72)
G2	56 (38.62)	28 (38.36)	28 (38.89)
G1	2 (1.38)	1 (1.37)	1 (1.39)
Receptor status			
ER+/PR+	83 (56.08)	41 (54.67)	42 (57.53)
ER−/PR−	47 (31.76)	27 (36.00)	20 (27.40)
ER+/PR−	15 (10.14)	4 (5.33)	11 (15.07)
ER−/PR+	3 (2.03)	3 (4.00)	0
HER2−	123 (87.86)	64 (87.67)	59 (88.06)
HER2+	17 (12.14)	9 (12.33)	8 (11.94)
Chemotherapy regime (at randomisation) according to current guidelines			
Epirubicin/cyclophosphamid/paclitaxel	53 (35.33)	27 (36.00)	26 (34.67)
Epirubicin/cyclophosphamid/docetaxel	32 (21.33)	15 (20.00)	17 (22.67)
5-Fluorourazyll/epirubicin/cyclophosphamid	30 (20.00)	15 (20.00)	15 (20.00)
5-Fluorourazyll/epirubicin/cyclophosphamid/docetaxel	26 (17.33)	13 (17.33)	13 (17.33)
Epirubicin/cyclophosphamid/trastzumab	9 (6.00)	5 (6.67)	4 (5.33)

28 patients) were hematoma (90%) and pain (2%). None of these AEs led to clinically relevant disease or was treated in the hospital.

Results of the qualitative study

A total of 20 patients (mean age 55 ± 9.6 SD) were interviewed. Of all contacted patients, two declined participation because of time constraints.

Relevance of the acupuncture treatment

All but one patient in the acupuncture group stated that the acupuncture treatment reduced symptoms triggered by chemotherapy. Patients reported reductions in headache, limb pain, gastrointestinal problems (e.g., nausea, taste, appetite, defecation) and polyneuropathy after acupuncture. In addition, the interviewed patients felt relaxed, less stressed, less fearful, psychologically stronger, and slept better. Moreover, acupuncture was said to support them

Table 3 Primary and secondary outcomes (means with 95% CI; adjusted for baseline value)

Primary and secondary outcome	3 months				6 months			
	Acupuncture mean [95% CI] $N=75$[c]	Control mean [95% CI] $N=75$[c]	Acupuncture vs. Control Difference mean [95% CI]	*p*-value	Acupuncture mean [95% CI] $N=75$[c]	Control mean [95% CI] $N=75$[c]	Acupuncture versus Control Difference mean [95% CI]	*p*-value
FACT-B total score[d]								
Intention-to-treat	105.5[b] [102.3;108.7]	104.6[b] [101.3;108.0]	0.9[b] [−3.8;5.5]	0.713[a]	103.5[a] [99.8;107.2]	101.4[a] [97.5;105.4]	2.0[a] [−3.4;7.5]	0.458[‡]
Sensitivity analyses								
Per protocol					103.8 [99.9;107.8]	102.1 [98.0;106.2]	1.7 [−4.0;7.4]	0.557
Intention-to-treat with imputation					102.6 [99.0;106.3]	100.2 [96.3;104.1]	2.4 [−2.9;7.7]	0.366
FACT-B subscales[b,d]								
Physical well-being subscale	22.3 [21.2;23.4]	20.7 [19.5;21.8]	1.6 [−0.0;3.3]	0.051	20.8 [19.6;22.1]	20.4 [19.1;21.7]	0.4 [−1.4;2.2]	0.653
Social/family well-being subscale	23.2 [22.4;24.0]	23.5 [22.6;24.3]	−0.3 [−1.5;0.9]	0.628	22.6 [21.7;23.6]	22.3 [21.2;23.3]	0.3 [−1.1;1.8]	0.638
Emotional well-being subscale	19.1 [18.3;19.9]	18.5 [17.7;19.4]	0.6 [−0.6;1.8]	0.337	19.4 [18.6;20.2]	18.9 [18.1;19.8]	0.5 [−0.7;1.6]	0.424
Functional well-being subscale	16.5 [15.4;17.6]	16.0 [14.9;17.2]	0.5 [−1.1;2.1]	0.540	16.7 [15.6;17.8]	16.0 [14.9;17.2]	0.6 [−1.0;2.2]	0.436
Breast cancer subscale	24.2 [23.3;25.1]	25.2 [24.3;26.2]	−1.0 [−2.3;0.3]	0.126	22.9 [21.7;24.2]	23.5 [22.1;24.8]	−0.5 [−2.4;1.3]	0.552
FACT-B single items[b,d]								
Pain[e]	0.5 [0.3;0.8]	0.8 [0.6;1.0]	−0.3 [−0.6;0.0]	0.095	0.9 [0.7;1.2]	0.8 [0.5;1.0]	0.2 [−0.2;0.5]	0.368
Sleep[f]	2.2 [2.0;2.5]	2.2 [1.9;2.4]	0.1 [−0.3;0.4]	0.793	2.3 [2.0;2.5]	2.1 [1.8;2.4]	0.2 [−0.2;0.5]	0.364
Nausea[e]	0.4 [0.2;0.6]	0.6 [0.4;0.9]	−0.3 [−0.6;0.0]	0.083	0.2 [0.0;0.3]	0.3 [0.1;0.5]	-0.1 [−0.4;0.1]	0.260
FACT/GOG-NTX Neurotoxicity Subscale[b,d]	39.1 [38.1;40.0]	39.0 [38.0;40.0]	0.1 [−1.4;1.5]	0.933	36.2 [34.7;37.7]	35.6 [34.0;37.2]	0.6 [−1.6;2.9]	0.588
FACIT-Fatigue subscale[bd]	37.1 [35.2;38.9]	35.1 [33.1;37.1]	2.0 [−0.8;4.7]	0.156	35.0 [32.7;37.2]	33.7 [31.3;36.1]	1.3 [−2.0;4.6]	0.438
Quality of life (SF-12)[bd]								
Mental component scale	48.0 [45.9;50.1]	47.7 [45.6;49.8]	0.3 [−2.7;3.2]	0.851	46.6 [44.1;49.0]	47.7 [45.1;50.2]	−1.1 [−4.6;2.4]	0.530
Physical component scale	44.6 [42.7;46.6]	43.9 [41.9;45.9]	0.7 [−2.1;3.5]	0.602	42.2 [39.9;44.6]	42.2 [39.7;44.6]	0.1 [−3.3;3.5]	0.972

CI confidence interval, *p* p-value for treatment effect

[a]Primary analysis of the primary endpoint

[b]Secondary endpoint

[c]Number of randomized patients (number of patients in analyses may vary, see Fig. 2). SF-12 = Short-Form Quality of Life Questionnaire (12 items). FACT-B Functional Assessment of Cancer Therapy-Breast, FACT-G Functional Assessment of Cancer Therapy-General, FACIT Functional Assessment of Chronic Illness Therapy

[d]Higher values indicate better Qol

[e]Higher score indicates worse feeling

[f]Higher score indicates better feeling

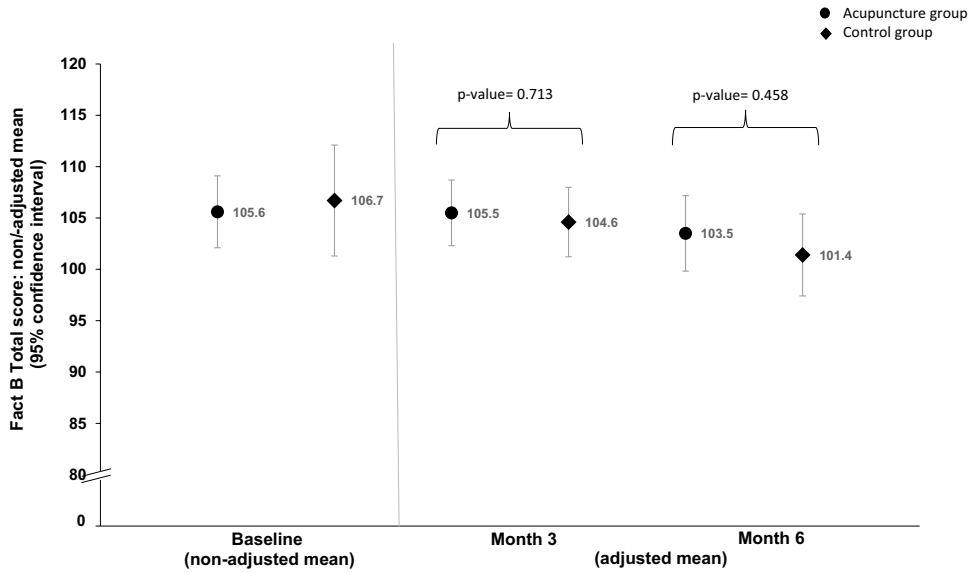

Fig. 2 Primary outcome parameter

Table 4 Adverse events of chemotherapy (reported in the hospital discharge letter)

	Total $N=133$ patients $n=1088$ AEs n (%)	Acupuncture $N=65$ patients $n=518$ AEs n (%)	Control $N=68$ patients $n=561$ AEs n (%)
Gastrointestinal disorders	387 (35.9)	178 (34.4)	209 (37.3)
General disorders and administration site conditions	268 (24.8)	130 (25.1)	138 (24.6)
Psychiatric disorders	87 (8.1)	45 (8.7)	42 (7.5)
Skin and subcutaneous tissue disorders	75 (7.0)	39 (7.5)	36 (6.4)
Vascular disorders	67 (6.2)	35 (6.8)	32 (5.7)
Respiratory, thoracic and mediastinal disorders	42 (3.9)	25 (4.8)	17 (3.0)
Nervous system disorders	41(3.8)	23 (4.4)	18 (3.2)
Infections and infestations	31(2.9)	10 (1.9)	21 (3.7)
Eye disorders	22 (2.0)	7 (1.4)	15 (2.7)
Blood and lymphatic system disorders	18 (1.7)	8 (1.5)	10 (1.8)
Cardiac disorders	11 (1.0)	6 (1.2)	5 (0.9)
Reproductive system and breast disorders	11(1.0)	3 (0.6)	8 (1.4)
Ear and labyrinth disorders	8 (0.74)	4 (0.77)	4 (0.71)
Musculoskeletal and connective tissue disorders	6 (0.56)	3 (0.58)	3 (0.53)
Metabolism and nutrition disorders	3 (0.3)	1 (0.2)	2 (0.4)
Immune system disorders	1 (0.1)	1 (0.2)	0 (0.0)
Renal and urinary disorders	1 (0.1)	0 (0.0)	1 (0.2)

Values are absolute numbers (n) and percentages (%)

in coping with the disease in a salutogenetic fashion. The acupuncture treatment was seen as an important opposite pole to the life-threatening disease and burdensome chemotherapy. This opposite pole was said to be directly experienced by a friendly setting, empathetic support by the acupuncture therapist, and the relaxation and enhancement of well-being during the treatment sessions.

Coping strategies

For patients in both groups, coping strategies with the cancer disease were essential during the study period. The issue of the prognosis of survival from the disease caused great emotional stress that seemed worse than the side effects. Simultaneously, they expressed the desire to keep a positive

attitude towards life and their healing process in the sense of *I gonna make it*. Chosen social contacts were seen as substantial support. In addition, patients tried to stay active as much as the occurrence of side effects allowed, e.g., keeping house, spending time outdoors, and exercising. Some patients even continued to work during the chemotherapy period.

Discussion

Breast cancer patients receiving prophylactic acupuncture during chemotherapy did not report better quality of life or a reduction in side effects of chemotherapy than did patients receiving no additional acupuncture. In contrast to these results, the majority of patients in the acupuncture group rated the effectiveness of acupuncture positively and was satisfied with the acupuncture treatment. Qualitative study results showed that patients in the acupuncture group reported positive effects on psychological and physical well-being. For both patient groups, coping strategies with the cancer disease were more important than reducing side effects.

To our knowledge, the present study was the largest randomized trial of prophylactic acupuncture in breast cancer patients who received chemotherapy for their newly diagnosed cancer. Following the methods of comparative effectiveness research, this randomized study took a pragmatic approach [35] in a usual care setting, aiming to evaluate the effects of acupuncture to improve quality of life and to prevent side effects of chemotherapy or to treat them as soon as possible. We used internationally established and accepted outcome parameters for breast cancer patients to evaluate possible acupuncture effects. Study data were analyzed in depth, including several sensitivity analyses for the primary endpoint and the per-protocol population without receiving different study results. We nested a qualitative study in the pragmatic study to obtain in-depth information regarding the non-selected BC patients who were randomized to both groups to interpret the study results with more care.

However, the pragmatic approach has methodological limitations: Neither patients nor study physicians were blinded to study intervention. Because the patients assessed all outcome parameters independently, patient bias toward the intervention generally cannot be ruled out. To minimize social acceptability bias, all questionnaires were sent directly from and were returned to the coordinating research institute. Moreover, the semi-standardized study intervention in our trial represented a compromise between flexibility (as desired by acupuncturists) and reproducibility (as desired by researchers). While these issues might be considered limitations from an experimental perspective, including lower internal validity, the study design was chosen to receive data regarding an often-used acupuncture treatment to simulate general medical practice as closely as possible and therefore to yield higher external validity. Another limitation was that we might have missed some information on adverse events because we gathered the information indirectly from the hospital discharge letter and not directly from the patients in real time by research staff as it would be common in a prospective clinical trial.

To date, acupuncture showed mainly positive effects in trials with cancer patients [19, 21]. Especially in breast cancer [22–24], beneficial effects of acupuncture were found in reducing side effects of chemotherapy such as nausea and vomiting [8–10, 12–16, 20, 36].

However, the results of the systematic reviews [22–24] were based on studies with heterogeneous designs and methodological quality, with sample sizes ranging from fewer than 20 patients to more than 600 patients, e.g., trials on nausea and vomiting reduction [19]. In addition, in trials with large sample sizes, acupuncture yielded less positive treatment effects than it did in trials with smaller samples sizes. In a systematic review of the effect of acupuncture on therapy-related adverse events in BC patients, 23/26 trials reported positive outcomes [22]. However, only nine trials were of high quality. The authors concluded that only for chemotherapy-induced nausea and vomiting (CINV) was there positive evidence for acupuncture and that for other side effects no conclusive statements could be made. In a systematic review from 2013, acupuncture was only recommended for reducing CINV [37]. By contrast to evidence based on three high-quality trials, we did not find substantial differences in chemotherapy-induced gastrointestinal symptoms between the acupuncture (35%) and the control group (37%) in our trial. A recent clinical practice guideline for breast cancer patients also recommended acupuncture for reducing CINV with a grade of B and for pain and quality of life with a grade of C [24].

Why are our results so different? In our pragmatic trial, we used only acupuncture and not electro-acupuncture, for which a positive result in a high-quality trial could be documented [9]. Electro-acupuncture was rated as more effective for reducing chemotherapy-induced nausea and vomiting in systematic reviews [37, 38]. Contrary to almost all other trials on acupuncture in breast cancer, in our study patients underwent prophylactic acupuncture in parallel to the chemotherapy and not only after symptoms had appeared. In our trial specific acupuncture point combinations were used for specific chemotherapy side effects if they occurred. In addition, because of the prophylactic approach, our patients were very heterogeneous in terms of number and severity of side effects they developed, with more or less impact on the primary outcome parameter (quality of life). However, in addition to the more difficult outcome measurement, it might

be that acupuncture was more effective when symptoms had already occurred than when preventing symptoms.

Acupuncture is often used not as a single intervention but rather as part of a complex CIM setting in BC patients, as it is also used normally in the Jerusalem Hospital. It was shown that a complex individualized CIM, including acupuncture, meditation, movement therapy, osteopathy, hyperthermia and herbal medicine including Chinese herbal medicine in addition to routine care had beneficial effects in BC patients [7]. In the present study, the qualitative study showed that, for both patient groups, coping strategies related to the cancer disease were more important than reducing side effects by acupuncture. This observation was supported by the overall positive assessment of the acupuncture treatment by the patients at the end of the trial and the results of the qualitative study.

The patient's general assessments of the treatment effect and the high satisfaction with the treatment in the acupuncture group, as well as the qualitative study results, contradict the other quantitative results. We can only speculate that the outcome measures with the FACT-B total score as primary endpoint and the secondary parameters may not have been sensitive enough or the measurement time points might have an influence, and more frequent measurements might be helpful to obtain a better understanding. Although our primary and secondary outcome parameters are internationally accepted and validated, other outcome maesures like the Edmonton Symptom Assessment System (ESAS), the MD Anderson Symptom Inventory (MDASI) and the Patient Reported Outcomes-Common Terminology Criteria for AE (Pro-CTCAE) may have been more sensitive and given other results. In addition, recruitment took much longer than expected because other breast cancer studies took place in parallel at the Jerusalem Hospital and recruitment staff was limited. Because of the extended recruitment period, a change in chemotherapy protocols occurred during the study period. Although the randomization process was stratified for the chemotherapy regime, the change of the chemotherapy and the use of five different chemotherapy regimens may also have influenced the results.

When using an open-label pragmatic trial design with a usual care control group, one would have expected at least a non-specific effect due to positive treatment expectations. However, we have no good explanation as to why this was not represented in the quantitative study results.

Conclusion

In this study, breast cancer patients receiving acupuncture as prophylaxis for chemotherapy-induced side effects in addition to standard cancer care did not report better quality of life or fewer chemotherapy-induced side effects than did patients without acupuncture treatment, in contrast to the reported positive effects in the qualitative interviews.

In addition, qualitative interviews revealed that, for both patient groups, coping strategies were more important during the study period than was a reduction in side effects.

Author contributions All authors participated in developing the study design and protocol and in revising the manuscript. Specific tasks and responsibilities: study conventionalization and general trial coordination (CW, BB), statistical expertise and analysis (SR, SB), data management (SB), study intervention (BK), and overall medical responsibility (MC). All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval All procedures performed in the study were in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards and with the local ethics review board (Ethic Committee of Medical Association Hamburg, Reference Number PV4002; June 2012). Because guidelines for chemotherapy treatment regime changed during the study and because of the inclusion of nested qualitative study, amendments were submitted and were approved in February 2014 and June 2016, respectively.

Research involving animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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