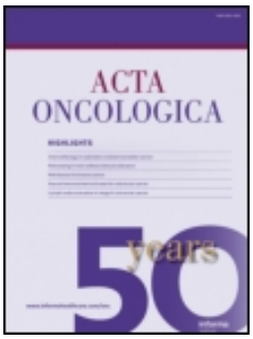

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ORIGINAL ARTICLE

Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: Cross-sectional findings from the neuropsychological TEAM-side study

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Abstract

Background. Previous studies have indicated that a subset of cancer patients treated with chemotherapy show cognitive deficits and/or experience cognitive complaints, whereas literature about the influence of hormonal therapies on cognition is sparse. Because of the accumulating knowledge about the importance of estrogen for cognitive functioning, there is growing concern about adjuvant hormonal therapy for breast cancer (BC) affecting cognition. We examined the cognitive functioning of postmenopausal BC patients who were, following doxorubicin/cyclophosphamide (AC) chemotherapy, randomized to tamoxifen or exemestane, and compared their performance with that of non-cancer controls. *Materials and methods*. Thirty BC patients using tamoxifen and 50 patients using exemestane underwent interviews, questionnaires and cognitive tests, on average two years after completion of AC chemotherapy. Forty eight healthy controls were tested with similar measures. *Results.* Memory complaints were reported by 28% of AC/tamoxifen users, 24% of AC/exemestane users and 6% of healthy controls ($p = 0.02$). Cognitive testing revealed no statistically significant differences between tamoxifen and exemestane users, but suggested that tamoxifen use is possibly related to worse verbal functioning, while exemestane use is possibly related to slower manual motor speed. Both patient groups performed significantly worse than healthy controls on verbal fluency and information processing speed. *Discussion.* Our findings show that sequential treatment of AC-chemotherapy and hormonal therapy in postmenopausal, primary BC is associated with lower test scores for certain cognitive functions, and provide indications for possibly distinctive associations for different types of hormonal treatment. Future research with larger groups is recommended to obtain a more definite picture.

Since the first publication in which comprehensive neuropsychological testing has been used, the literature describing relationships between adjuvant cytotoxic regimens and cognitive functioning is accumulating rapidly. A recent meta-analysis using seven cross-sectional studies suggests small to medium cumulative effect-sizes across eight cognitive domains, with lower cognitive functioning for breast cancer (BC) patients compared to healthy controls [1]. In recent years, several prospective longitudinal studies are published, of which most, but not all, found subtle negative influences of chemotherapy on cognitive functioning in a subset of patients [2]. The etiology of cognitive impairment during and/or after chemotherapy remains unknown although a number of mechanisms, for example direct neurotoxic effects, oxidative stress and DNA damage, induced hormonal changes, immune dysregulation and/or release of cytokines, and blood clotting in small CNS vessels have been postulated. A number of possible confounding factors hereby exist although it is suggested that mood/emotional status, menopausal status, fatigue and physical functioning do not drive the relation between adjuvant chemotherapy

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and cognitive impairment [2]. These factors however, may, well be related to self-reported cognitive problems in daily life [3].

A large proportion of patients treated with chemotherapy will receive anti-estrogenic hormonal therapy additionally, often for years. As a result of increasing knowledge about the possible effects of estrogens on the brain and cognitive functioning, it has been questioned whether and how adjuvant hormonal therapies for BC are affecting cognitive functions [4,5]. Possibly beneficial effects of estrogens on brain function may be among others the result of estrogenic activity through estrogen receptors (ER) in brain regions that are important for cognitive functioning, effects on neurotransmitters, protection against ischemic damage and increased survival of brain cells [6]. The widely used selective estrogen receptor modulator (SERM) tamoxifen exerts anti-estrogenic effects on BC cells that contain estrogen receptors by blocking this receptor, and therefore inhibiting the binding of estrogens. On other tissues, for example bone and endometrium, tamoxifen has also estrogenic activities. Whether tamoxifen has estrogenic or anti-estrogenic qualities on brain tissue is insufficiently known. Evidence for a detrimental effect of tamoxifen on memory has been reported in animal studies with mice [7]. With respect to BC patients, cognitive impairment associated with tamoxifen use is not yet well distinguished from cognitive impairment associated with chemotherapy and conflicting results are reported [3,8]. Further, the influence of tamoxifen on cognitive functioning when chemotherapy is not administered also is uncertain due to lack of a specific study hereon. Limited cognitive assessment was performed as part of a mailed questionnaire by Paganini-Hill & Clarck [9]. They found no clear differences in test performances between tamoxifen- and non-tamoxifen users, although more women who had used tamoxifen for five years or longer reported seeing their physician for memory problems than non-users. Further evidence for anti-estrogenic effects in the brain was found in a neuro-imaging study (using PET and MRI), whereby tamoxifen users showed widespread area's of hypometabolism and a trend towards smaller right hippocampal volumes relative to non-users and estrogen users [10]. Opposite results [11] were found in a proton magnetic resonance spectroscopy study comparing brain metabolism in tamoxifen-users with estrogen-users and controls. In both tamoxifen and estrogen-users, lower concentrations of myo-inositol (a brain marker that is associated with brain damage) were found than in the controls, suggesting that tamoxifen and estrogen have similar (possibly protective) effects on brain functioning.

Over the recent years, aromatase inhibitors (AI) are increasingly used as adjuvant hormonal therapy by postmenopausal, hormone sensitive BC patients either as upfront treatment or after 2–3 years of tamoxifen. These agents (anastrozole, letrozole, exemestane) reduce the postmenopausal estrogen levels by nearly complete inhibition of the enzyme aromatase. Their effect on cognitive functioning is by now largely unknown. Only for anastrozole, preliminary data from two small studies have been published, showing impaired performance among anastrozole users with regard to verbal memory and information processing speed [12] and verbal and visual memory [13].

The goals of the current cross-sectional study were: (1) to study differences in cognitive performance of postmenopausal BC patients, randomly assigned to tamoxifen and exemestane after adjuvant doxorubicin and cyclophosphamide (AC) chemotherapy. (2) to compare cognitive functioning of postmenopausal BC patients treated with AC-chemotherapy followed by hormonal therapy with cognitive functioning of a healthy, control group of the same age-range.

Materials and methods

Participants & procedure

This cross-sectional study was conducted in the context of a larger, prospective neuropsychological study into the cognitive effects of hormonal therapy in postmenopausal BC patients. Participants of both the prospective as well as the present cross-sectional study are patients from the Tamoxifen and Exemestane Multicenter Trial (TEAM trial, an open label, randomized multi center comparative trial of 5 years adjuvant therapy with exemestane versus 2.5 years with tamoxifen followed by exemestane for 2.5 years). In the prospective neuropsychological study, patients who were not qualified to receive chemotherapy participated. The present, cross-sectional study was conducted among patients of 13 Dutch community hospitals who received AC-chemotherapy before the start of hormonal therapy. Inclusion criteria for the TEAM-trial were: (1) histologically/cytologically confirmed adenocarcinoma of the breast followed by intended curative surgery; (2) tumor size >3 cm, or any N+, or tumor size 1–3 cm and one of the following:-MAI >10,-grade 3 according to Bloom-Richardson,-any TNM stage BC considered to receive adjuvant hormonal therapy; (3) ER and/or PgR status positive; (4) being postmenopausal; (5) adequate hematological, renal and hepatic function and (6) an Eastern Cooperative Oncology Group (ECOG) performance of 0 or 1.

Exclusion criteria were: (1) palliative treatment, inflammatory breast cancer, positive supraclavicular nodes or ulceration/infiltration of local skin metastasis; (2) evidence of distant metastases; (3) previous adjuvant hormonal treatment; (4) uncontrolled cardiac disease; (5) psychiatric disorders preventing proper informed consent; (6) concomitant malignancies or other significant malignancies within the past 5 years; (7) or other serious illnesses; (8) HRT use not stopped at least 4 weeks prior to randomization; (9) bilateral tumor; (10) neo-adjuvant chemotherapy. For the current neuropsychological side study additional inclusion criteria were: (1) free of CNS disease; (2) no signs of dementia according to a dementia screenings tool (7 minutes screen) [14]; (3) being fluent in Dutch; and (4) use of the originally assigned hormonal agent for at least six months. The population of the present study consisted of three groups: a group of BC patients who received tamoxifen after completion of AC-chemotherapy, a group who received exemestane after AC-chemotherapy and a healthy comparison group. At the time of investigation, being on average 2 years after completion of chemotherapy, all patients were clinically free of disease. A comparison group of healthy women was derived from an existing group of female friends and relatives of the BC patients participating in the prospective neuropsychological study of the TEAM trial. The recruitment of healthy controls took place through invitation by the patients of the prospective study. Patients were asked to invite a female friend or relative of approximately the same age to participate in the study and provided us contact information of interested women. Inclusion criteria for controls were: postmenopausal status, no history of CNS or malignant disease and fluent in the Dutch language. From this healthy control group, persons out of the age- and IQ-ranges of the patients of the current study were selected. Written informed consent was obtained from all participants. The ethical committees of all participating hospitals approved the study. Cognitive testing was conducted by experienced and trained research assistants.

Measures

Self-reported cognitive functioning. All participants were interviewed concerning cognitive complaints in daily life, regarding memory, concentration, thinking and language. The frequency of reported problems was scored as a number on a 5-point Likert scale (0 = never; 1 = once in a while; 2 = regularly; 3 = often; 4 = always) [15]. In addition, the women filled out the Cognitive Failures Questionnaire (CFQ) [16], a 25 item questionnaire regarding cognitive failures in daily life. In this questionnaire, the frequency of common lapses with regard to memory and attention is rated on a 4-point scale, ranging from 'never' to 'always'.

Health-related quality of life, anxiety/depression, fatigue, menopausal symptoms. Health related quality of life was assessed by means of the EORTC quality of life questionnaire (QLQ-C30) [17], that incorporates functional scales and scales/items to assess symptoms and global quality of life. Anxiety/depression was assessed with the Hopkins Symptom Checklist-25 (HSCL) [18]. To assess fatigue, the multidimensional fatigue inventory [19] (MFI-20) was included in the study, while menopausal symptoms were assessed by the Endocrine Subscale of the Functional Assessment of Cancer Therapy – Breast questionnaire (FACT-B ES) [20].

Cognitive tests. A comprehensive test battery was designed to assess a broad range of eight specific cognitive domains, comprising 18 test indices [21–29] (see Table I). Besides these outcome-variables, the Dutch Adult Reading Test [30] was used as a measure of pre-morbid verbal intelligence. Also, a dementia-screening tool was included to detect participants with signs of beginning dementia (7-minutes screen [14]). The tests were selected for reliability, validity, sensitivity for effects of hormones and suitability for older age groups.

Data analysis. The Statistical Package for Social Sciences (SPSS) WINDOWS 15.0 was used for statistical analyses. The data from the questionnaires were converted to scores according to standard scoring rules. Differences in sociodemographic characteristics between groups were analyzed by means of Chi-square tests for contingency tables or univariate analysis of variance. Differences between groups in scales from questionnaires were determined by univariate analysis of variance (ANOVA). To compare overall cognitive functioning between tamoxifen and exemestane users (goal 1), we performed multivariate analysis of variance (MANOVA) across all 18 cognitive test variables. Follow-up univariate analyses of variance (ANOVA) were conducted to determine the differences between separate tests. Both the MANOVA as well as the ANOVA's were adjusted for age, IQ and time since completion of chemotherapy.

MANOVA and subsequent ANOVA's, adjusted for age and IQ, were used to compare cognitive functioning between patients and healthy controls. In addition to the comparison of mean test scores,

Table I. Summary of cognitive test measures and outcome variables.

Cognitive domain	Cognitive tests	Outcome variable	Score range
Verbal memory	Rey auditory verbal learning test[21] (Dutch shortened version)	1. Total of 3 trials	0–45
		2. Total for long delay trial	0–15
Visual memory	Wechsler Memory Scale revised – visual memory subtest[22]	3. Immediate recall	0–41
		4. Delayed recall	0–41
	Visual Association Test[23]	5. Total of 2 trials	0–24
Working memory	WAIS III Letter-number sequencing[24]	6. Total correct trials	0–21
Attention/ concentration	Stroop Card 1[25]	7. Seconds to complete	0+
	Stroop Card 2[25]	8. Seconds to complete	0+
	Trailmaking A[26]	9. Seconds to complete	0+
Mental Flexibility	Stroop Card 3[25]	10. Seconds to complete	0+
	Trailmaking B[26]	11. Seconds to complete	0+
Speed of information processing	Fepsy Reaction times: [27]		
	1. dominant hand	12. Mean msec/30 trials	0+
	2. non-dominant hand	13. Mean msec/30 trials	0+
Manual motor speed	Fepsy Finger tapping: [27]		
	1. dominant hand	14. Mean score of 5 trials of 10 seconds	0+
	2. non-dominant hand	15. Mean score of 5 trials of 10 seconds	0+
Verbal fluency	Letter fluency (D,A,T) [29]	16. Total score of 3 letters/1 minute each	0+
	Category Fluency (Animals/ professions)[28]	17. Total score animals/1 minute	0+
		18. Total score professions/1 minute	0+

we determined the proportion of cognitively impaired persons in both patient groups and the control group. Cognitive test scores were converted into Z-scores using the mean and standard deviation (SD) of the healthy controls. When necessary, transformations were made so that higher Z-scores represented better performance. We considered failure on a test if the score was two standard deviations below the mean of the healthy control group [28]. An overall impairment score was calculated for each patient by counting all tests on which the patient was impaired. The fifth percentile of the overall impairment scores of the healthy controls was used as a cut-off score to distinguish between normal and impaired cognitive functioning [3]. Differences in proportions were tested with logistic regressions. Although differences in age and IQ between the three groups were not statistically significant, we chose to adjust for age and IQ in the analyses because age and IQ are strong predictors for test performance.

Associations between neuropsychological test performance and anxiety/depression, fatigue, menopausal symptoms, time since completion of chemotherapy and reported cognitive complaints in daily life were analyzed using Pearson's correlation coefficients. For those analyses, we used the mean Z-score of all test indices as a measure of overall cognitive functioning. A two-sided p-value less than 0.05 was required for statistical significance, but for the 18 cognitive outcome measures, we applied a Bonferroni correction to adjust for multiple comparisons, requiring a two-sided p-value of less than .0028 for statistical significance. Effects-sizes are calculated with Cohen's *d* and based on the partial eta squared after adjustment for age, IQ and (for the comparisons between tamoxifen and exemestane users) time since chemotherapy.

Results

Patient enrolment

Ninety-six patients were eligible for the study, 34 receiving tamoxifen and 62 receiving exemestane. These group sizes were unbalanced because patients who were assigned to tamoxifen but after 2–2.5 years had switched to exemestane according to the TEAM protocol were not eligible anymore, while patients who were assigned to exemestane remained eligible after 2–2.5 years. Twelve percent of the tamoxifen users (n = 4) and 16% of the exemestane users (n = 10) declined to participate, one patient had too serious problems with word finding to participate in the study and one was excluded due to multiple sclerosis, eventually leaving 80 patients (30 tamoxifen; 50 exemestane) eligible for analysis. The decliners were slightly older than the participants (mean age 60.3 and 58.3 years respectively).

With regard to the healthy controls, no information was available on the number of approached controls by the patients. Of the healthy control women who provided contact information, none declined participation. Three participants in the

Table II. Sociodemographic characteristics of patients and controls.

	AC/Tam (n = 30)	AC/Exe (n = 50)	Controls (n = 48)	P-value
Mean age, yrs (SD)	57.9 (3.9)	58.5 (5.4)	60.2 (5.1)	0.10
range	49–65	48–71	49–71	
Level of education (%, n)				
Low	20 (6)	12 (6)	13 (6)	0.46
Middle	67 (20)	68 (34)	58 (28)	
High	13 (4)	20 (10)	29 (14)	
IQ estimate	98.7 (13.7)	104.0 (17.6)	103.0 (15.6)	0.36
Current treatment for:				
- high blood pressure (%, n)	13 (4)	22 (11)	25 (12)	0.46
- diabetes mellitus (%, n)	0 (0)	8 (4)	6 (3)	0.30
HRT use				
- previous (%, n)	23 (7)	38 (19)	21 (10)	0.13
- current (%, n)	0 (0)	0 (0)	4 (2)	
- never (%, n)	77 (23)	62 (31)	75 (36)	
Current use of				
- anti-depressive medication (%, n)	7 (2)	6 (3)	0 (0)	0.21
- benzodiazepines (%, n)	20 (6)	18 (9)	8 (4)	0.27
- cholesterol lowering agents (%, n)	7 (2)	4 (2)	13 (6)	0.28
Mean time since completion of chemotherapy (yrs, SD)	1.9 (0.5)	2.4 (0.7)	–	0.002
Past radiotherapy (%, n)	83 (25)	80 (40)	–	0.78

AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen; AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane; SD = standard deviation.

healthy control group used some type of hormonal treatment (two used HRT, one used a progestin). One participant had two missing test scores; estimates on the base of age and IQ were imputed for that participant using an expectation-maximization (EM) algorithm. According to the 7-minute screen test, none of the participants had signs of a beginning dementia.

Sociodemographic characteristics

The two patient groups and the healthy control group were well balanced with respect to demographic and medical history variables. With regard to clinical variables, the two patient groups only differed significantly on time since chemotherapy, i.e. longer time for exemestane users (Table II).

Self-reported complaints of cognitive functioning

Significantly more patients than healthy controls reported having complaints about their daily memory functioning (patients: 25%; healthy controls: 6%), but the proportion of patients reporting memory complaints did not differ between patients receiving tamoxifen (28%) and exemestane (24%). Regarding complaints about concentration, thinking and language and the cognitive failures self-report scale (CFQ), there were no differences between the three groups (Table III).

Health related quality of life, anxiety and depression, fatigue and menopausal symptoms

For none of the EORTC-QLQ-C30 subscales statistical significant differences between tamoxifen and

Table III. Self reported cognitive problems in daily life[a].

	AC /Tam (n = 30)	AC /Exe (n = 50)	Controls (n = 48)	P-value
Memory (%, n)	28 (8)[b]	24 (12)	6 (3)	0.02
Concentration (%, n)	21 (6)[b]	18 (9)	13 (6)	0.60
Thinking (%, n)	7 (2)	6 (3)	2 (1)	0.55
Language (%, n)	17 (5)	10 (5)	2 (1)	0.34
CFQ[c] (mean; SD)	33.8 (9.3)	36.7 (11.2)	32.6 (7.6)	0.11

AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen; AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane; SD = standard deviation.

[a]Patients who rated the frequency of their cognitive problem as at least 2 ('regularly') in a distinct domain were considered as having a complaint.

[b]n = 29.

[c]Range 0–100, higher scores means higher frequency of cognitive lapses in daily life.

Table IV. Health related quality of life (EORTC-QLQ-C30), Anxiety and Depression (HSCL), Fatigue (MFI) and Menopausal symptoms (FACT-B ES). Left side: AC/tamoxifen users versus AC/exemestane users; Right side: combined patient group versus healthy controls.

	AC/Tam (n = 30) Mean (SD)	AC/Exe (n = 50) Mean (SD)	P-value[f]	Effect-size[g]	Combined patient group (n = 80) Mean (SD)	Controls (n = 48) Mean (SD)	P-value	Effect-size[g]
EORTC-QLQ-C30								
Function Scales[a]								
Physical	83.8 (14.9)	86.7 (14.4)	.54	.14	85.6 (14.6)	87.2 (15.0)	.54	.11
Role	81.1 (23.0)	84.0 (23.6)	.83	.05	82.9 (23.3)	89.9 (19.7)	.08	.31
Cognitive	79.4 (23.0)	80.3 (20.9)	.86	.04	80.0 (21.6)	92.0 (12.9)	.001	.62
Emotional	84.7 (20.2)	84.3 (15.8)	.74	.08	84.5 (17.4)	85.8 (17.2)	.69	.07
Social	91.7 (21.3)	89.3 (18.1)	.56	.13	90.2 (19.2)	93.4 (14.9)	.33	.18
Global QoL	79.2 (17.6)	81.2(17.2)	.99	.00	80.4 (17.3)	85.2 (16.7)	.12	.28
Symptom scales/items[b]								
Fatigue	28.5 (20.6)	23.8 (21.4)	.55	.14	25.6 (21.1)	15.0(12.7)	.002	.56
Nausea and vomiting	6.1 (18.8)	3.3 (8.2)	.56	.13	4.4 (13.2)	1.4 (4.7)	.13	.27
Pain	22.2 (27.8)	18.3 (24.6)	.81	.05	19.8 (25.7)	19.1 (27.5)	.89	.03
Dyspnea	16.7 (21.0)	6.7 (16.5)	.05	.45	10.4 (18.8)	6.3 (14.8)	.19	.23
Sleep disturbance	37.8 (31.2)	31.3 (31.2)	.38	.20	33.8 (31.1)	18.8 (26.5)	.006	.50
Appetite loss	8.9 (19.4)	6.0 (17.4)	.46	.17	7.1 (18.1)	4.2 (16.3)	.36	.16
Constipation	4.4 (14.5)	7.3 (15.5)	.27	.25	6.3 (15.1)	4.2(11.1)	.41	.15
Diarrhea	2.2 (8.5)	3.3 (15.4)	.36	.21	2.9 (13.2)	2.1 (8.2)	.69	.07
Financial impact	2.2 (8.5)	4.0 (12.8)	.27	.26	3.3 (11.3)	1.4 (6.7)	.28	.19
HSCL[b]								
Anxiety	14.7 (9.0)	10.2 (9.9)	.20	.29	11.9 (9.87)	9.9(11.0)	.28	.19
Depression	13.5 (9.9)	13.1 (9.9)	.81	.06	13.2 (9.8)	9.8 (10.8)	.07	.33
MFI								
General fatigue[c]	10.6 (4.1)	9.2 (3.9)	.38	.20	9.7 (4.0)	7.6(3.1)	.002	.56
Physical fatigue[c]	9.6 (4.7)	8.7 (4.1)	.97	.01	9.0 (4.3)	7.9 (3.5)	.12	.28
Reduction of activities[c]	9.2 (4.5)	9.2 (4.1)	.46	.17	9.2 (4.2)	7.3 (2.9)	.006	.49
Reduction of motivation[c]	8.8 (3.4)	7.9 (3.4)	.56	.13	8.3 (3.4)	6.5 (3.0)	.004	.52
Mental fatigue[c]	10.5 (4.1)	9.7 (4.5)	.85	.04	10.0 (4.3)	8.7 (3.8)	.10	.29
FACT-B ES total score[d]	57.7 (8.2)	57.0 (9.1)	.38	.20	57.3 (8.7)	62.1 (6.1)	.001	.60

AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen; AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane; SD = standard deviation; EORTC = European Organization for Research an Treatment of Cancer; EORTC QLQ-C30 is a health-related quality of life questionnaire; HSCL (Hopkins Symptom Check-list-25) is a anxiety/depression symptom checklist; MFI = multi-dimensional fatigue inventory is a questionnaire addressing several dimensions of fatigue, FACT B ES the Endocrine Subscale of the Functional Assessment of Cancer Therapy – Breast questionnaire for assessment of menopausal symptoms (see 'Materials and methods' section for more details).

[a] Higher scale means better functioning; scale 0–100. [b] Higher score means more serious complaints; scale 0–100. [c] Higher score means more serious complaints; scale 4–20. [d] Higher score means less serious complaints; scale 0–72. [f] P-value adjusted for time since completion of chemotherapy. [g]Cohen's *d:* <.50: small effect, .50–.80: medium effect, >.80: large effect, range 0–2.

exemestane users were observed (Table IV). The comparison between the combined patient groups and healthy controls revealed significantly lower scores on the cognitive functioning scale for patients ($p \leq 0.001$, $d = 0.62$). On the symptom scales, patients reported more fatigue ($p = 0.002$, $d = 0.56$) and sleep disturbances ($p = 0.006$, $d = 0.50$) than healthy controls. There were no differences between the three groups with regard to symptoms of anxiety and depression (HSCL). With regard to menopausal symptoms (FACT-B ES) patients reported more problems than healthy controls ($p = 0.001$, $d = 0.60$), particularly on the items 'hot flashes', 'cold sweats' and 'night sweats'.

Cognitive test performance

Overall cognitive functioning was not significantly different between tamoxifen and exemestane users (MANOVA $F = 1.33$; $p = 0.21$). Subsequent univariate ANOVA's did not reveal a significant difference for any of the 18 test scores (Table V, left side). Effect-sizes were, in general, small. Mean scores of exemestane users were generally slightly better (although not statistically significant) on tests with a language component (verbal memory tests, verbal fluency tests, Stroop-test) and slightly worse on several tests with a motor-speed component (tapping test and Trailmaking test) compared to tamoxifen-users.

Table V. Cognitive test scores (raw test scores). Left side: AC/tamoxifen users versus AC/exemestane users; Right side: combined patient group versus healthy controls.

Cognitive domains and tests (see table 1 for more details)	AC/Tam (n = 30) Mean (SD)	AC/Exe (n = 50) Mean (SD)	P-value*	Effect-Size[g]	Combined patient group (n = 80) Mean (SD)	Controls (n = 48) Mean (SD)	P-value**	Effect-size[g]
Verbal memory								
RAVLT immediate [#]	21.2 (5.1)	22.8 (4.7)	.22	.29	22.2 (4.9)	23.5 (5.2)	.08	.31
RAVLT delayed [¥]	6.6 (2.2)	7.0 (2.2)	.42	.19	6.8 (2.2)	7.3 (2.9)	.21	.22
Visual memory								
Visual Association Test [¥]	20.5 (2.9)	21.5 (2.3)	.16	.33	21.1 (2.5)	21.3 (2.4)	.54	.11
WMS Visual memory immediate [¥]	32.9 (5.8)	32.6 (4.7)	.57	.13	32.7 (5.1)	33.6 (4.4)	.16	.25
WMS Visual memory delayed [¥]	29.4 (7.3)	29.2 (6.8)	.36	.21	29.3 (7.0)	30.7 (5.3)	.10	.30
Working memory								
Letter Number Sequencing [¥]	9.7(2.1)	10.1 (2.4)	.64	.11	9.9 (2.3)	9.8 (2.4)	.79	.05
Attention/Concentration								
Stroop Card 1[§]	48.7 (8.1)	44.8 (6.1)	.13	.36	46.3 (7.2)	46.1 (7.5)	.86	.03
Stroop Card 2 [§]	62.2 (9.9)	58.1 (9.0)	.16	.33	60.0 (9.5)	60.1 (9.6)	.97	.01
Trailmaking A[§]	36.5 (13.8)	40.3 (16.4)	.07	.43	38.9 (15.5)	36.0 (10.5)	.12	.28
Mental flexibility								
Stroop Card 3 [§]	108.7 (22.0)	97.7 (22.5)	.07	.42	101.8 (22.8)	96.4 (18.2)	.02	.43
Trailmaking B [§]	82.6 (25.2)	86.8 (35.3)	.08	.40	85.2 (31.8)	82.1 (31.7)	.21	.23
Information Processing Speed								
RT - dominant hand [‡]	355 (84)	339 (66)	.62	.12	345 (73)	316 (47)	.01	.47
RT - non-dominant hand [‡]	340 (98)	347 (68)	.74	.08	344 (80)	304 (53)	.002	.56
Motor Speed								
Tapping dominant hand [!!]	60.2 (8.3)	59.0 (8.4)	.24	.28	59.4 (8.3)	54.9 (8.2)	.01	.45
Tapping non-dominant hand [!!]	53.9 (7.5)	53.2 (7.8)	.50	.16	53.4 (7.7)	50.4 (7.3)	.06	.34
Verbal Fluency								
Category fluency - animals [ŧ]	21.4 (4.1)	23.0 (5.6)	.42	.19	22.4 (5.2)	25.5 (6.3)	.001	.60
Category fluency - professions [ŧ]	16.6 (4.0)	17.4 (4.6)	.66	.10	17.1 (4.4)	20.9 (6.0)	<.001	.80
Letter fluency (DAT)[ŧ ŧ]	33.5 (9.3)	39.0 (10.9)	.14	.34	36.9 (10.7)	39.5 (11.9)	.14	.27

[a]AC/Tam = doxorubicin/cyclophosphamide chemotherapy followed by tamoxifen; [b] AC/Exe = doxorubicin/cyclophosphamide chemotherapy followed by exemestane; SD = standard deviation; * adjusted for age/IQ/time since completion chemotherapy; ** adjusted for age/IQ. [#]total number of words after 3 trials; [¥]number of correct responses; [§]seconds to complete task (lower scores represent better performance); ‡ milliseconds (lower scores represent better performance); [!!]mean of 5 trials of 10 seconds; [ŧ]total of words produced in one minute; [ŧ ŧ]total number of words produced in 3 minutes (1 minute for each letter). [g] Cohen's *d:* <.50: small effect, .50–.80: medium effect, >.80: large effect, range 0–2.

Comparison of overall cognitive functioning between the total patient group and the healthy control group showed worse cognitive functioning of patients (MANOVA F = 2.80, p = 0 .001). Univariate ANOVA's suggest that two category fluency tests (animals: p = 0.001; d = 0.60; professions: p ≤ 0.001; d = 0 .80) and one information processing speed tests (non-dominant hand, p = 0 .002; d = 0 .56) discriminated best between patients and healthy controls (Table V, right side).

The proportions of persons that were classified as cognitively impaired according to the definition did not differ between groups (healthy controls: 4%, n = 2; tamoxifen users: 3%, n = 1; exemestane users: 6%, n = 3, data not shown).

Relationships between cognitive functioning, self-reported cognitive complaints, anxiety, depression, fatigue, menopausal complaints and time since completion of chemotherapy

Self-reported frequency of cognitive lapses (CFQ) show significant correlations with anxiety (r = 0.35), depression (r = 0.45), fatigue (r = 0.55) and menopausal symptoms (r = 0.35), but not with overall cognitive performance and time since completion of chemotherapy. Anxiety, depression, fatigue and menopausal symptoms are strongly intercorrelated (r varying from 0.56 to 0.68). Better overall cognitive performance is weakly related to less fatigue (r = 0.23) and a longer time since completion of chemotherapy (r = 0.22). In addition, weak

correlations exist between time since completion of chemotherapy and anxiety ($r = 0.25$), fatigue ($r = 0.27$) and cognitive performance ($r = 0.22$) (data not shown).

Discussion

There is growing evidence for cognitive dysfunction during and/or after adjuvant systemic treatment for BC, but associations between different hormonal treatments and cognitive functioning have not yet been thoroughly studied. The present study does not reveal clear differences in cognitive performance between tamoxifen and exemestane users after exposure to AC-chemotherapy. However, exploratory analyses suggest that for most tests with a verbal component (verbal memory, verbal fluency, Stroop test) exemestane users outperformed tamoxifen users, while for several tests with a manual motor-speed component (tapping, Trailmaking test) tamoxifen users performed better than exemestane users. Although speculative because of the small and non-significant differences, an explanation could be that tamoxifen and exemestane potentially have distinctive effects on different cognitive domains. Distinctive effects between tamoxifen and aromatase inhibitors are theoretically possible given the different mechanisms of action, but this issue is hardly studied until now. Only one, very small study reported on distinctive effects of tamoxifen and anastrozole, suggesting poorer verbal and visual memory for anastrozole users [13]. From our data, a different picture arises, suggesting that tamoxifen is associated with worse verbal functioning while exemestane negatively is associated with worse manual motor speed. Because a negative impact on musculoskeletal function has been described for aromatase inhibitors [4], it is possible that motor speed-deficits in exemestane users are rather a musculoskeletal feature than a cognitive problem. So, this should be taken into account in further cognitive studies.

While clear differences in cognitive functioning between tamoxifen users and exemestane users were lacking in our patient groups, differences between the combined patient group and healthy controls were present. Treatment with AC-chemotherapy followed by hormonal therapy is associated with a lower level of cognitive performance. The cognitive domains that show significant differences are verbal fluency and information processing speed. These findings are consistent with earlier studies, although deficits in other domains (for example visual memory) also have been described [2]. A remarkable finding in this analysis is that, although mean scores of several tests differ between the groups, we did not observe differences in the proportions of cognitively impaired persons. This suggests that the combination of AC-chemotherapy and hormonal therapy is related to subtle cognitive impairment in a substantial part of the patients instead of substantial cognitive impairment in a small subgroup of patients. This finding differs from earlier studies that often showed clear differences in proportions of impaired patients while differences in mean test scores are rather small [15].

Because we made use of a healthy, non-cancer control group, it is possible that being diagnosed as a cancer patient, or surgical and/or radiotherapeutic procedures influence cognitive performance of the patients. An earlier study showed that a breast cancer control group who did receive radiotherapy but no systemic treatment did not score different from published test norms and concluded that it is unlikely that cognitive impairment is a consequence of these factors [15]. Nevertheless, due to the cross-sectional nature of the study, we can not rule out the possibility that pre-treatment differences between the patients and the healthy controls have influenced the differences in cognitive performance found.

With respect to self-reported cognitive functioning, our study shows, which is consistent with previous studies [3] that a higher proportion of treated patients experienced memory problems in daily life compared to healthy controls. The proportion was not different between tamoxifen and exemestane users. Self-reported cognitive functioning in our data is, consistent with previous data [3,8], related to anxiety, depression and fatigue, but not with cognitive test performance. Furthermore, cognitive test performance is not related to anxiety and depression.

Strengths of this study are the randomized attribution of the hormonal agents and the homogeneity with regard to the used chemotherapy regimen. Furthermore, inclusion of a control group enabled us to consider cognitive performance, psychological functioning and 'quality of life'-data of BC patients within the perspective of daily functioning of healthy postmenopausal women.

However, our study also has several limitations. First, the sample sizes of each of the groups are relatively small and unbalanced, and second, the patient groups differed with respect to time since completion of chemotherapy. These differences were particularly a result of our inclusion criteria: patients allocated to tamoxifen treatment were not eligible after their switch to exemestane, while patients

allocated to exemestane were eligible irrespective of time on treatment. The difference in time since chemotherapy might be of influence on cognitive performance. However, it is unclear in what direction this influence would be, and for which treatment group this might be beneficial. A longer time since chemotherapy means also a longer time since diagnosis and surgery, but also a longer time on hormonal treatment and a longer survival time. Because we did not know to what extent and in which direction these differences might influence our results, we considered 'time since completion of chemotherapy' as a confounder and adjusted for it in all comparisons between the two patient groups. Third, because of the cross-sectional nature of the study, corrections for pre-treatment differences between the groups could not be made, changes in cognitive function over time could not be studied and causal relationships between treatments and cognitive functioning could not be established. Forth, our study did not include a patient group treated with only AC-chemotherapy and no hormonal therapy. Therefore, it was not possible to distinguish between the effects of AC-chemotherapy and the effects of hormonal therapy. From the literature, data on the specific cognitive sequelae after standard dosed AC-chemotherapy in postmenopausal BC patients are not available either.

Our study provides additional data supporting the fact that systemic therapy for BC is associated with subtle cognitive impairment in postmenopausal patients, although our data does not give evidence for a particular subgroup of patients with outlying test scores. Of interest, our study suggests that tamoxifen and exemestane potentially exert distinctive effects on cognitive functioning, maybe related to different mechanisms of action, i.e. anti-estrogenic as well as estrogenic effects for tamoxifen versus blocking of estrogen production for exemestane. To unravel the separate effects of chemotherapy and hormonal therapy, and to establish causal relationships between these systemic treatment and cognitive functioning, larger prospective neuropsychological studies are needed in patients who are qualified to receive hormonal therapy only, and patients who are qualified to receive chemotherapy only.

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