Cognitive function in older women with breast cancer treated with standard chemotherapy and capecitabine on Cancer and Leukemia Group B 49907

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Abstract

Cognitive changes in older women receiving chemotherapy are poorly understood. We examined self-reported cognitive function for older women who received adjuvant chemotherapy on Cancer and Leukemia Group B (CALGB) 49907. CALGB 49907 randomized 633 women aged 65 with stage I–III breast cancer to standard adjuvant chemotherapy (cyclophosphamide–methotrexate–5-fluoro-uracil or doxorubicin–cyclophosphamide) versus capecitabine. We examined self-reported cognitive function in 297 women (CALGB 361002) who enrolled on the quality of life substudy and had no gross impairment on cognitive screening. Women were evaluated using an 18-item instrument at six time points (baseline through 24 months). At each time point for each patient, we calculated a cognitive function score (CFS) defined as the mean response of items 1–18 and defined impairment as a score >1.5 standard deviations above the overall average baseline score. Differences in scores by patient characteristics were evaluated using a Kruskal–Wallis test. A linear mixed-effects model was used to assess CFSs by treatment over time. Among 297 women, the median age was 71.5 (range 65–85) and 73 % had performance status of 0. Baseline depression and fatigue were reported in 6 and 14 % of patients, respectively. The average CFS at baseline was 2.08 (corresponding to "normal ability"), and baseline cognitive function did not differ by treatment regimen ($p = 0.350$). Over 24 months, women reported minimal changes at each time point and insignificant differences by treatment arm were observed. In a healthy group of older women, chemotherapy was not associated with longitudinal changes in self-reported cognitive function.

Keywords

Cognitive function; Older women; Breast cancer; Age

Introduction

The majority of breast cancer diagnoses occur in older women [1], many of whom will be recommended to receive chemotherapy to lower their risk of disease recurrence. Although many toxicities of chemotherapy have been well elucidated for younger women, the side effects that older women experience are less defined, largely as a result of the underrepresentation of older women in most clinical trials. There has been some suggestion that older patients experience greater chemotherapy-related toxicity compared with younger women, despite similar risk reductions in relapse-free and overall survival with treatment [2, 3]. However, the extent of cognitive decline in older women who receive chemotherapy remains poorly studied.

The potential for "chemo-brain" and "chemo-fog," terms often used to describe the cognitive changes women report while receiving chemotherapy, is of great concern to the patient and survivorship community and is a widely discussed entity in the media and cancer literature [4, 5]. Prior studies have reported variable cognitive changes in 15–50 % of cancer patients who undergo chemotherapy [6–13], with observed difficulties in attention, learning, and processing speed during treatment [11] that typically improve over time [9, 14]. The risk factors for developing cognitive changes during cancer-directed therapies are unknown but may include specific treatments (high-dose chemotherapy, bone marrow transplant) [15, 16],

genetic predisposition [17], menopausal symptoms [13], inflammatory markers [18], depression [16], fatigue [19], and other potential factors, particularly age [20–22]. However, studying changes in cognitive function is challenging, particularly because the changes observed on objective testing of cognition often do not correlate with subjective report and may not fully reflect patients' experiences [10, 23–26]. Self-reported changes in cognitive function during and after chemotherapy are associated with psychological distress, quality of life, health status, and fatigue [6, 19, 27].

Small studies in populations of older patients receiving chemotherapy have shown conflicting results on whether cognitive dysfunction is a significant clinical problem, and longitudinal assessments have not been consistently included [21, 28–32]. In the quality of life substudy Cancer and Leukemia Group B (CALGB) 361002, we examined changes in a self-reported cognitive function scale in older women with breast cancer who received adjuvant chemotherapy on CALGB protocol 49907. CALGB 49907 randomized women to receive standard chemotherapy (either cyclophosphamide–methotrexate–5-fluorouracil [CMF] or doxorubicin–cyclophosphamide [AC] by provider choice) or capecitabine [33]. This study, one of the few prospective trials dedicated to older patients, demonstrated superiority in relapse-free survival and overall survival for patients treated with standard chemotherapy compared with capecitabine. Multiple preplanned, prospective, ancillary studies were embedded within 49907, including examination of quality of life (QOL) [34]. For the QOL substudy, the first 368 women who spoke English or Spanish were asked to participate. The longitudinal data collection for the QOL substudy provided a unique opportunity to conduct a secondary analysis of cognitive function for older women who received chemotherapy. We assessed longitudinal, subjective changes in cognitive function for 297 women on the QOL substudy (CALGB 361002).

Patients and methods

Population and data collection

CALGB 49907 enrolled 633 patients aged 65 during 2001–2006 at 149 nationwide centers with the objective of evaluating the potential noninferiority of an oral, potentially less toxic adjuvant chemotherapeutic agent (capecitabine) to standard chemotherapy (CMF or AC, by provider choice). Patients were eligible for the parent study if they had at least a 1-cm, operable, invasive breast cancer with negative surgical margins and no distant metastases, Eastern Cooperative Oncology Group performance status of 0–2, adequate organ function, expected survival of more than 5 years, and no medical condition that would make protocol treatments unreasonably hazardous. Women were excluded because of a concurrent malignancy or a previous cancer with a risk of relapse >30 %. The full details of eligibility for CALGB 49907 have been previously published [33]. Treatment arms were assigned randomly in a 1:1 fashion to standard chemotherapy (CMF or AC) or capecitabine.

The QOL companion study simultaneously enrolled 350 of the first 368 patients on CALGB 49907 between 2002 and 2006 randomized to either standard chemotherapy ($n = 182$) or capecitabine ($n = 168$) [34]. Women signed an institutional review board–approved informed consent prior to participation. Patients were English- or Spanish-speaking and passed an initial screening to rule out gross cognitive impairment using the Blessed Orientation-Memory-Concentration (BOMC) test [35]. Those scoring 11 or higher on the BOMC ($n = 17$) were considered to have significant impairment, making them ineligible. Survey data regarding social support, stressful life events, toxicity, changes in physical function, adherence to therapy, and neurobehavioral symptoms were collected on the QOL study at six time points: (1) baseline, (2) mid-treatment, (3) within 1 month post-treatment, (4) 12 months, (5) 18 months, and (6) 24 months. Results of the QOL substudy have been previously published [34].

Among the 350 patients who participated in the QOL study, 334 patients completed at least one assessment of cognitive function; 10 missed the baseline evaluation and 27 missed all five follow-up assessments. These 37 patients were excluded from analyses with a final sample size of 297 women (Fig. 1). The reasons for missing questionnaires over time often corresponded to the timing of stopping protocol therapy and included the following: disease progression ($n = 1$), toxicity ($n = 8$), death on study ($n = 2$), patient withdrawal after starting or prior to starting treatment ($n = 6$), per protocol ($n = 7$), and other/missing reason ($n = 3$). There were no withdrawals for cognitive toxicity specifically.

Measures

The Neurobehavioral Functioning and Activities of Daily Living (NBFADL) scale is a 60-item scale that has been previously used and validated to assess cognitive issues in daily life that affect functioning [36, 37]. The Memory, Cognitive and Concentration subscales of the NBFADL were selected for the QOL study as a subjective cognitive function measure and were administered as a telephone survey at all six time points along with the other components of the QOL study. Patients who consented to participate were given a packet of QOL questionnaires to complete before the telephone interview, at which time the centralized research interviewer collected their answers [34]. The subscales included 18 questions that evaluated five domains of cognitive function including attention, problem-solving, speed, new learning and prospective memory, and remote memory (Table 1). Patients selected a response for each question ranging from 1 to 7 (1 = "above average" to 7 = "severe problems").

Variables of interest

The primary variable of interest was cognitive function score (CFS), defined as the mean response of items 1–18 from the Memory, Cognitive and Concentration subscale of the NBFADL scale. Cognitive impairment was defined as a CFS at any time point that was >1.5 standard deviations (SDs) above the overall average baseline score [14].

Patient characteristics evaluated for association with CFS included treatment arm assignment, treatment regimen, age, number of comorbid conditions according to the Older American and Services (OARS) Questionnaire [38, 39], hormonal therapy, education level, and stage of disease. Because of potential impact on cognitive function, we also examined the occurrence of depression, anxiety, and fatigue at baseline according to the European Organization for the Research and Treatment of Cancer (EORTC) Quality of Life (QLQ-C30) questionnaire [40, 41] and the Hospital Anxiety and Depression Scale (HADS) [42]. The QLQ-C30 is a 30-question measure on global health status, function, and symptoms, and it also includes two items on attention and memory. The HADS is a 14-question measure on the frequency of depression- and anxiety-related symptoms (i.e., "I get sudden feelings of panic" and "I look forward with enjoyment to things"). We defined the presence of depression at baseline if participants answered "quite a bit" or "very much" to either of the mood questions on the EORTC QLQ-C30 ("Over the last week, did you feel irritable?… did you feel depressed?") or had a HADS score 11 on the depression subscales. Baseline anxiety was defined as a HADS score 11 on anxiety subscales [42]. Fatigue was defined by having answered "quite a bit" or "very much" to a single question on the EORTC measure ("Were you tired?") [41].

Statistical analysis

Frequency distributions and means were used to describe baseline patient characteristics. Associations among groups for categorical variables were assessed with chi-square and Fisher's exact tests. The differences in CFSs and baseline characteristics among groups were compared with a Kruskal–Wallis test. For univariate analyses, we used a 0.05 type 1 error

rate. A linear mixed-effects model with nominal time to each assessment as the repeated variable was used to assess the differences in CFSs among treatment arms, assuming a compound symmetric covariance structure and assuming that any missing data were missing at random. All available data were used in the analyses of cognitive function over time. Covariates included in the model were age, assessment, treatment arm, and an interaction term between treatment arm and assessment. The type 1 error rate was adjusted to 0.01 to reduce the chance of spurious significant findings. In addition, baseline characteristics for women with<20 % missing data versus those with ≥20 % missing data (i.e., women with 1–4 follow-up assessments missing after baseline) were compared. There were no differences in baseline characteristics for women by the degree of missing data, with the exception of rates of hormone receptor (HR)-positive status (72 % had HR-positive disease in those with <20 % missing data versus 60 % with HR-positive disease in those with ≥20 % missing data, $p = 0.041$). An exploratory analysis was performed on the women with baseline scores >1.5 SDs from the group baseline mean ($n = 19$) to determine how they differed from the remaining cohort. Frequency distributions were used to describe cognitive impairment over time.

Lastly, because our 18-item measure has not been validated previously outside of the comprehensive NBFADL scale, we used Pearson correlations to examine whether the EORTC questions for attention and memory impairment ("Have you had difficulty in concentrating on things, like reading a newspaper or watching television?" and "Have you had difficulty remembering things?") correlated with our results from the NBFADL-based CFS. For the correlation analysis, we averaged the scores between the two EORTC questions and then converted to a 100-point scale as described in the EORTC scoring manual [41]. All statistical analyses were performed by Alliance statisticians using SAS v9.2 (Cary, NC, USA).

Results

There were 367 (350 eligible) women enrolled to the QOL portion of CALGB 49907 from June 2002 through April 2006. Characteristics of the 297 women in this study are displayed in Table 2. The median age of participants was 71.5 years (range 65–85). Over 70 % of women had a performance status of zero, and 30 % reported four to ten comorbidities [38, 39]. Approximately 51 % of women reported having a high school education or less. Baseline anxiety, depression, and fatigue were uncommon. Approximately 21 % of women received AC, 32 % received CMF, and 47 % received capecitabine. Baseline characteristics did not differ for women by treatment regimen received, with the exception of fatigue (i.e., 21 % for CMF, 8 % for AC, and 13 % for capecitabine, $p = 0.049$). Of note, with the exception of differences in age, patients included in this study were similar to women who enrolled on the treatment component for CALGB 49907 (mean age 71.9 years for women on this study versus 73.0 years on treatment component, $p = 0.004$).

At baseline, the average CFS was 2.08 (range 1.00–5.56), corresponding to nearly "normal ability." Women with worse cognitive function at baseline were less educated ($p = 0.003$) and had more positive nodes ($p = 0.022$), more comorbid conditions ($p = 0.002$), more fatigue ($p = 0.020$), and more anxiety ($p = 0.010$), although numerical differences between subgroups were small (average CFSs range = 1.77–2.37 across all categories, corresponding to "normal ability") (Table 2). There were no differences in baseline CFSs by treatment regimen ($p = 0.350$).

During the study period, the overall average CFSs by treatment arm remained within "normal ability" (Table 3). At mid-treatment, within 1 month post-treatment, and at 12, 18, and 24 months, adjusted CFSs ranged from 2.1 to 2.3. Results from the linear mixed-effects

model also showed little variation in self-reported CFSs over time (Table 3). There were no differences by treatment arm (Fig. 2) over time).

Cognitive impairment was observed in 19 (6 %) women at baseline, 19 (6 %) at mid-treatment, 29 (10 %) at the end of the treatment, 31 (12 %) at 12 months post-treatment, 18 (7 %) at 18 months post-treatment, and 22 (9 %) at 24 months post-treatment. At 24 months, 14 of the 19 women had measures completed at both baseline and 24 months. Of these women, nine reported impairment (64 %) at both time points. Although relative impairment was observed in these patients by our definition, the numerical differences between time points for nearly all patients were small.

Finally, the Pearson correlation coefficients for mean self-reported CFSs and the memory and attention components of the EORTC were calculated at each time point and ranged in magnitude from 0.539 to 0.680 (data not shown). These observations indicate that in general, women who reported good memory and attention on the EORTC also reported good cognitive function on the Neurobehavioral Scales form (and vice versa).

Discussion

We examined self-reported cognitive function for a prospective, large cohort of older women with breast cancer who received adjuvant chemotherapy on a clinical trial. In this healthy, older population with primarily normal self-reported cognitive function at baseline, we observed minimal changes in cognitive function over time and minimal differences in subjective cognitive function by treatment received. At 24 months, nearly all patients reported normal cognitive function.

Prior studies on cognitive function changes in older women receiving systemic therapy have shown variable results and have generally included small samples of women without multiple longitudinal assessments or consistent inclusion of subjective report. Hurria et al. [21] examined objective cognitive function in 31 patients aged 65 and older who received adjuvant chemotherapy for breast cancer and demonstrated objective declines in cognitive function in 25 % of patients (defined as a difference in 1 SD in 2 or more domains on neuropsychological testing) from before chemotherapy to 6 months after completion of chemotherapy, and 50 % reported subjective decline in cognitive function, which was most pronounced in patients who reported pre-existing memory problems. Another study assessed cognitive function longitudinally in older women undergoing chemotherapy and found significant changes in processing speed and verbal ability compared with controls. Impairment was worse among older women, although the mean age was 55 years and only 60 women received chemotherapy [20].

A meta-analysis assessing 30 cognitive function studies including over 800 women receiving adjuvant chemotherapy for breast cancer showed only modest changes in verbal and visuospatial ability for women on treatment. In this analysis, no differences by age were observed, although the median age for women included in the analysis was 52.3 years [15]. Yamada et al. performed a focused examination for longer-term effects in 30 older women who received chemotherapy 10 years prior to enrollment. Here, women who received chemotherapy performed worse on objective cognitive function testing compared with matched controls [29], demonstrating the importance of following women over time. Overall, because of the small sample sizes and variable methodological approaches of these studies, the evidence for cognitive function changes remains controversial and definitive data are lacking.

Our study is the largest, prospective study to date of cognitive function in older women receiving chemotherapy and included six time points, allowing for examination of the entire

treatment and post-treatment trajectory. We also had individual information on comorbidity, baseline cognitive function, tumor characteristics, and presence of fatigue, depression, and anxiety, which are all factors that may impact cognitive function. Nevertheless, our study has some limitations. First, we studied a highly selected population of older women in a randomized trial who were healthy enough to receive chemotherapy and who passed an initial cognitive function screening test, excluding women with gross cognitive dysfunction. In addition, women had good performance status and organ function. Although our findings cannot be generalized to all older patients, our observations are very relevant to healthy, older women who are typically selected to receive chemotherapy. Second, our analyses did not allow a comparison of cognitive function with a control group of older breast cancer patients not receiving chemotherapy, a control group of older noncancer patients, or a control group of younger women to assess impact of having cancer and/or cancer therapy as well as age. Others have noted that a cancer diagnosis itself may have adverse effects on cognition apart from any anxiety, fatigue, or depression [11, 19, 43, 44]. We also could not evaluate age–treatment interactions since all patients were 65 and older. Ahles et al. [20] have noted such interactions, and these will be important to confirm in future research. Third, assignment to treatment with AC versus CMF within the standard treatment arm was not random but was selected by providers, which may influence findings, although cognitive function changes were rare for all study participants regardless of treatment received. Fourth, our assessments of cognitive function have not been previously validated as a measure independent from the complete NBFADL and are self-reported only. However, arguably, how women feel about their cognitive changes may be more important from a quality of life standpoint than any objective changes observed, and others have documented the poor correlation between objective and subjective cognitive functional decline [10, 23–26]. Lastly, because few women met the criteria for cognitive impairment and because differences in scores over time were small, our ability to perform analyses assessing factors associated with such impairment was limited.

In summary, older women on CALGB 49907 tolerated standard and nonstandard chemotherapy without subjective declines in cognitive function over the first 24 months after starting treatment. Although our study included a selected population of older women, these findings are reassuring because of the concerns for cognitive decline in older women receiving cancer-directed systemic therapy. Future studies should include consistent, prospective, detailed subjective and objective assessments of cognitive and physical function to further expand our knowledge about how our treatments impact older women with breast cancer. Systematic studies on the various effects of chemotherapy on older patients will be necessary to optimally serve and support this growing population of patients.

Acknowledgments

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                    │ randomized in CALGB 49907│
                    │          N=633           │
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                    ┌─────────────────────────┐
                    │   Patients enrolled in   │
                    │ Quality of Life sub-study│
                    │          N=367           │
                    └─────────────────────────┘
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	Missing all assessments	N=16
	Missing baseline assessment	N=10
	Missing all follow-up assessments	N=27

Ineligible N=17

Eligible N=350

Included in cognitive function analysis N=297

Standard Chemotherapy (AC or CMF) N=157

Capecitabine N=140

Number of Neurobehavioral Assessments Completed

	Standard Chemotherapy
Baseline	n=157
Mid-Treatment	n=146 (93%)
End of Treatment	n=146 (93%)
12 month	n=135 (86%)
18 month	n=132 (84%)
24 month	n=131 (83%)

Number of Neurobehavioral Assessments Completed

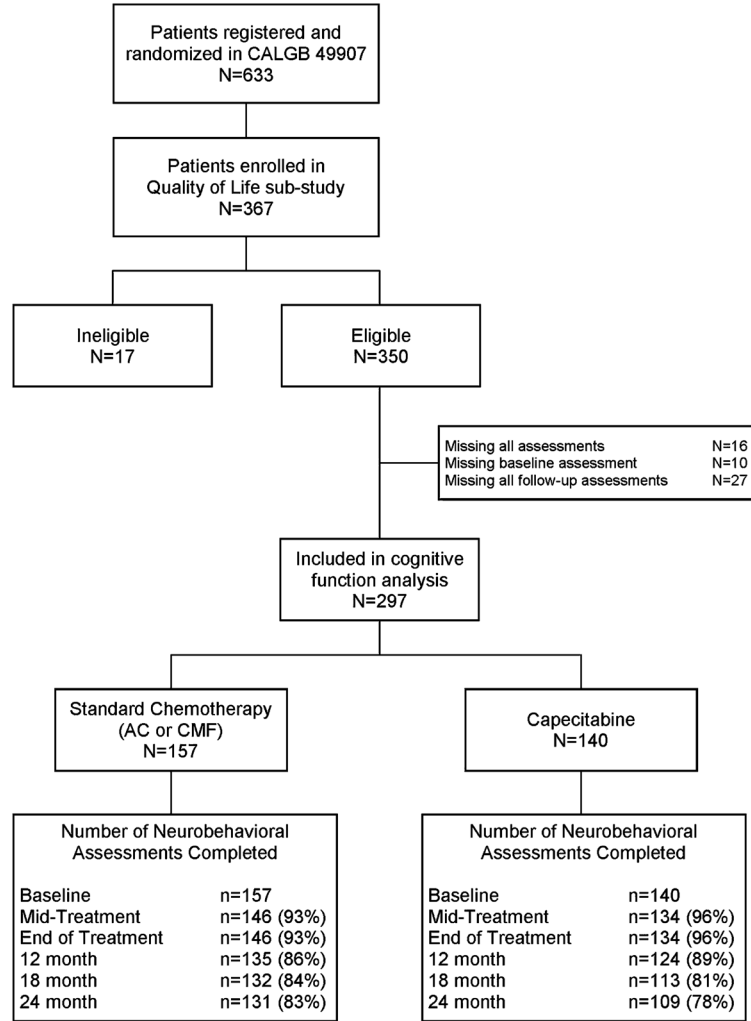|	Capecitabine
Baseline	n=140
Mid-Treatment	n=134 (96%)
End of Treatment	n=134 (96%)
12 month	n=124 (89%)
18 month	n=113 (81%)
24 month	n=109 (78%)

Fig. 1.
Neurobehavioral assessments completed over the study period. *Seventeen patients were deemed ineligible because they did not pass the Blessed Orientation-Memory-Concentration test at screening
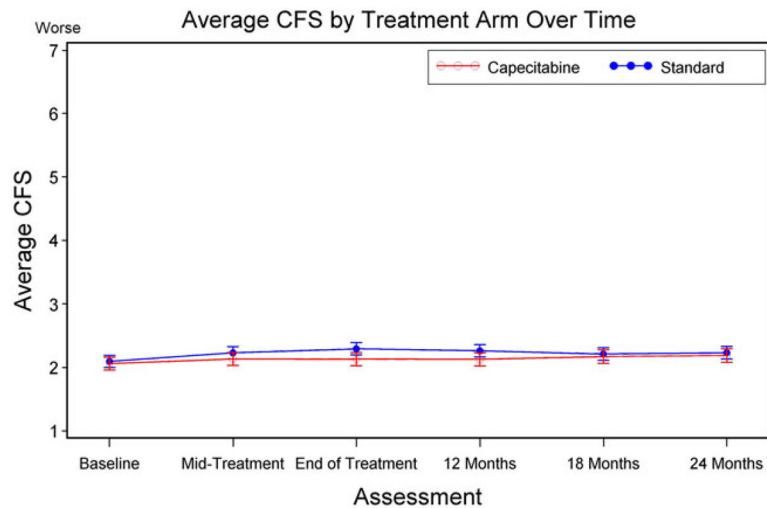
Fig. 2.
Mean cognitive function score (CFS) by treatment arm over time. Mid-treatment, doxorubicin–cyclophosphamide (AC): day 29; end of treatment, AC: 4–5 months. Mid-treatment, cyclophosphamide–methotrexate–5-fluorouracil (CMF): day 77; end of treatment, CMF: 6–7 months. Mid-treatment, capecitabine: day 63; end of treatment, capecitabine: 4–5 months. *Error bars* represent 95 % CI for the adjusted average cognitive function score (CFS)

Table 1

Questions and instructions from the 18-question measure

Neurobehavioral Scales form (domain assessed)	
1	Ability to avoid losing train of thought; distractibility (attention)
2	Ability to focus on goals; carry out a plan (problem-solving)
3	Remembering events from long ago (remote memory)
4	Remembering new information told to you (new learning and prospective memory)
5	Attention and concentration (attention)
6	Ability to reason through a complicated problem (problem-solving)
7	Self-awareness of problems (problem-solving)
8	Remembering what you intended to do (new learning and prospective memory)
9	Ability to shift easily from one activity to the next (problem-solving)
10	Remembering appointments or meetings (new learning and prospective memory)
11	General alertness (attention)
12	Ability to think clearly (attention)
13	Remembering new information you have read (new learning and prospective memory)
14	Remembering where you put things (new learning and prospective memory)
15	Ease in initiating or starting activities by oneself (speed)
16	Ability to make decisions (problem-solving)
17	Remembering information learned long ago (new learning and prospective memory)
18	Ability to be flexible, rather than rigid or have overly set manner (problem-solving)

Patients were asked to "mark an X in a single box indicating the appropriate response for each task [marked 1–7]"

Response options for each item ranged from 1 to 7 and included the following: 1 = above average, 2 = normal ability, 3 = mild problem, 4 = mild to moderate problem, 5 = moderate problem, 6 = moderate to severe problem, 7 = severe problem

Table 2

Baseline cognitive function score by patient characteristics ($n = 297$)

Variable	N (%)	Baseline cognitive function score[a] (standard deviation)	p value[b]
Age			0.598
65–69 year	120 (40)	2.05 (0.43)	
70–79 year	166 (56)	2.10 (0.59)	
80 year	11 (4)	1.95 (0.28)	
Race			0.118
White	259 (87)	2.05 (0.47)	
Black	32 (11)	2.27 (0.81)	
Other	3 (0)	2.07 (0.47)	
Unknown	3 (0)	2.37 (0.36)	
Education			0.003
Grades 1–11	35 (12)	2.33 (0.74)	
High school graduate	115 (39)	2.09 (0.42)	
Some college/junior college	82 (27)	2.06 (0.51)	
College/post-college/advanced	59 (20)	1.96 (0.51)	
Degree unknown	6 (2)	1.77 (0.60)	
Tumor size			0.787
2 cm	129 (43)	2.07 (0.44)	
2–5 cm	156 (53)	2.10 (0.59)	
>5 cm	11 (4)	1.96 (0.38)	
Number of positive lymph nodes			0.022
0	88 (30)	2.03 (0.55)	
1–3	164 (55)	2.05 (0.44)	
4+	44 (15)	2.27 (0.69)	
Stage			0.228
I	21 (7)	1.88 (0.45)	
IIA	117 (39)	2.11 (0.53)	
IIB	92 (31)	2.11 (0.58)	
IIIA	20 (7)	1.96 (0.32)	
IIIB	1 (<1)	2.67 (n/a)	
Unknown	46 (15)	2.05 (0.44)	
Hormone receptor status[c]			0.150
Negative	95 (32)	2.06 (0.65)	
Positive	202 (68)	2.08 (0.45)	
HER2 status			0.379
Negative	234 (79)	2.07 (0.45)	
Positive	44 (15)	2.18 (0.80)	
Unknown	19 (6)	1.97 (0.51)	
ECOG performance status			0.265
0 (Normal)	218 (73)	2.03 (0.42)	

Variable	N (%)	Baseline cognitive function score[a] (standard deviation)	p value[b]
1 (Ambulatory)	74 (25)	2.22 (0.72)	
2 (<50 % time in bed)	5 (2)	2.21 (0.53)	
Treatment arm			0.619
Standard (AC or CMF)	157 (53)	2.10 (0.46)	
Capecitabine	140 (47)	2.06 (0.58)	
Treatment received			0.350
AC	95 (32)	2.08 (0.51)	
CMF	62 (21)	2.11 (0.37)	
Capecitabine	140 (47)	2.06 (0.58)	
Tamoxifen use			0.527
No	238 (80)	2.08 (0.54)	
Yes	58 (21)	2.08 (0.44)	
Unknown	1 (0.4)	1.22 (not applicable)	
OARS number of comorbidities			0.002
0	24(8)	1.93 (0.40)	
1	36 (21)	1.94 (0.42)	
2–3	120 (40)	2.06 (0.47)	
4–10	90 (30)	2.24 (0.63)	
Fatigue			0.020
No	252 (85)	2.05 (0.50)	
Yes	40 (13)	2.30 (0.64)	
Unknown	5 (2)	1.99 (0.09)	
Depression			0.276
No	280 (94)	2.07 (0.52)	
Yes	17 (6)	2.20 (0.43)	
Anxiety			0.010
No (score <11)	271 (91)	2.05 (0.48)	
Yes (score 11)	26 (9)	2.40 (0.74)	

ER estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *ECOG* Eastern Cooperative Oncology Group, *AC* doxorubicin plus cyclophosphamide, *CMF* cyclophosphamide–methotrexate–5-fluorouracil, *OARS* Older American Resources and Services, *HADS* Hospital Anxiety and Depression Scale, *EORTC* European Organization for the Research and Treatment of Cancer

[a] Possible scores ranged from 1 to 7 (1 = above average and 7 = severe problem)

[b] For differences in mean cognitive function score at baseline, by Kruskal–Wallis tests

[c] Hormone receptor (HR) status defined as the following: negative = ER-negative and PR-negative; positive = ER-positive and PR-positive, ER-negative/missing and PR-positive, or ER-positive and PR-negative/missing

Table 3

Adjusted cognitive function scores by treatment over time (linear mixed-effects model)

Assessment	Overall		Standard chemotherapy[a]		Capecitabine[b]		p value[c]
	CFS	SE	CFS	SE	CFS	SE	
Baseline	2.08	0.04	2.10	0.05	2.06	0.05	0.605
Mid-treatment	2.18	0.04	2.23	0.05	2.13	0.05	0.172
End of the treatment	2.21	0.04	2.29	0.05	2.13	0.05	0.024
12 months	2.19	0.04	2.21	0.05	2.17	0.05	0.573
18 months	2.19	0.04	2.23	0.05	2.19	0.05	0.546
24 months	2.21	0.04	2.26	0.05	2.13	0.05	0.065

Higher score = worse cognitive function. Covariates are age, treatment arm, assessment, and assessment–treatment arm interaction *CFS* cognitive function score, *SE* standard error

[a] For standard treatment with doxorubicin and cyclophosphamide (AC), mid-treatment, day 29; end of the treatment, 4–5 months; for treatment with cyclophosphamide, methotrexate, and fluorouracil (CMF): mid-treatment, day 77; end of the treatment, 6–7 months

[b] For treatment with capecitabine: mid-treatment, day 63; end of the treatment, 4–5 months

[c] *p* value compares standard and capecitabine treatment arms; a type 1 error rate was adjusted to 0.01 to reduce the chance of spurious significant findings