Original Article

Patterns of Change in Cognitive Function With Anastrozole Therapy

Catherine M. Bender, PhD, RN[1]; John D. Merriman, PhD, RN[1]; Amanda L. Gentry, MPH[1]; Gretchen M. Ahrendt, MD[2]; Sarah L. Berga, MD[3]; Adam M. Brufsky, MD, PhD[2]; Frances E. Casillo, RN, BSN[1]; Meredith M. Dailey, RN[1]; Kirk I. Erickson, PhD[1]; Frances M. Kratofil, RN[1]; Priscilla F. McAuliffe, MD, PhD[2]; Margaret Q. Rosenzweig, PhD, CRNP-C[1]; Christopher M. Ryan, PhD[1]; and Susan M. Sereika, PhD[1]

BACKGROUND: The purpose of this study was to examine and compare the effects of the first 18 months of anastrozole therapy on cognitive function in women with breast cancer. **METHODS:** This large, longitudinal cohort study was composed of postmenopausal women with early-stage breast cancer who received chemotherapy plus anastrozole (n = 114) or anastrozole alone (n = 173) and a control group (n = 110). Cognitive function was assessed before systemic therapy and 6, 12, and 18 months after therapy initiation and at comparable time points in controls. **RESULTS:** The chemotherapy-anastrozole and anastrozole-alone groups had poorer executive function than the controls at nearly all time points ($P < .0001$ to $P = .09$). A pattern of deterioration in working memory and concentration was observed during the first 6 months of anastrozole therapy for the chemotherapy-anastrozole group ($P < .0001$ and $P < .0009$, respectively) and the anastrozole-alone group ($P = .0008$ and $P = .0002$, respectively). This was followed by improved working memory and concentration from 6 to 12 months in both groups. The anastrozole-alone group had a second decline in working memory and concentration from 12 to 18 months after the initiation of therapy ($P < .0001$ and $P = .02$, respectively). **CONCLUSIONS:** Women with breast cancer had poorer executive functioning from the period before therapy through the entire first 18 months of therapy. A pattern of decline in working memory and concentration with initial exposure to anastrozole was observed. Women receiving anastrozole alone had a second deterioration in working memory and concentration from 12 to 18 months after therapy initiation. The longer term effects (>18 months) of anastrozole on cognitive function remain to be determined. ***Cancer* 2015;121:2627-36.** © *2015 American Cancer Society.*

KEYWORDS: anastrozole, breast cancer, chemotherapy, cognitive function, endocrine therapy.

INTRODUCTION

Even though more than 70% of women with breast cancer receive adjuvant endocrine therapy (ET), few studies have examined the specific influence of ET on cognitive function in this population. Most research on ET-associated cognitive changes has focused on selective estrogen receptor modulators and particularly tamoxifen.[1,2] Few studies have examined cognitive function with aromatase inhibitors (AIs), which are more commonly used in postmenopausal women. To date, study results have been inconsistent, partly because of methodological differences.[3-10] Among the few prospective studies,[8,11] the sample sizes were small, and some participants had begun ET at the baseline assessment; thus, there was no true pretreatment cognitive evaluation. Finally, to our knowledge, no studies have examined the potential contribution of chemotherapy to the influence of ET on cognitive function in women with breast cancer.

Multiple mechanisms, including changes in reproductive hormones, likely underlie cognitive declines in women with breast cancer (Fig. 1). AIs provide almost complete estradiol withdrawal by blocking the aromatase enzyme,[12] and we found that lower estradiol was associated with poorer psychomotor efficiency, attention, and executive function with therapy.[13]

We also found poorer cognitive function with anastrozole versus tamoxifen in a small cross-sectional study.[14] We now report the results of a large cohort study of postmenopausal women with early-stage breast cancer who received chemotherapy plus anastrozole or anastrozole alone versus a control group of women without breast cancer. The purpose of this study was to examine and compare the effect of anastrozole on cognitive function in these 3 cohorts before therapy and 6, 12, and 18 months after therapy commenced and at comparable time points in controls. We hypothesized that women

Corresponding author: Catherine Bender, PhD, RN, University of Pittsburgh, 3500 Victoria Street, Suite 415, Pittsburgh, PA 15201; Fax: (412) 383-7293; cbe100@pitt.edu

[1]University of Pittsburgh, Pittsburgh, Pennsylvania; [2]University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; [3]Wake Forest School of Medicine, Winston-Salem, North Carolina

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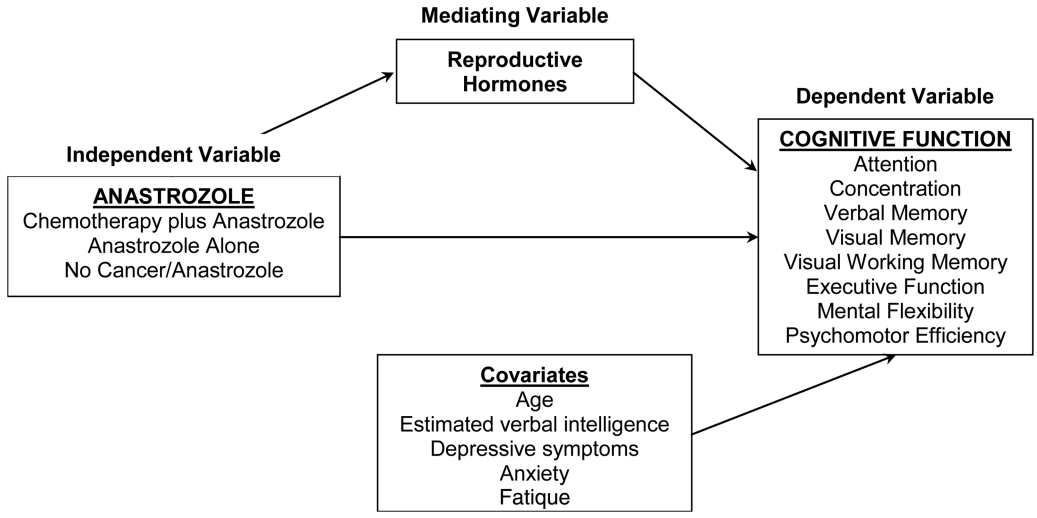

Figure 1. Hypothesized mechanism for the influence of anastrozole on cognitive function.

TABLE 1. Time Points per Group

Group	Before Chemotherapy	Before Anastrozole	6 Months After Anastrozole Initiation	12 Months After Anastrozole Initiation	18 Months After Anastrozole Initiation
Chemotherapy plus anastrozole	X	X	X	X	NA
Anastrozole alone	NA	X	X	X	X
Controls	X	X	X	X	X

Abbreviation: NA, not applicable.

with breast cancer would experience cognitive decline with anastrozole and that their cognitive function would be poorer than that of controls over time.

MATERIALS AND METHODS

Women with breast cancer were recruited from the Comprehensive Breast Cancer Program of the University of Pittsburgh Cancer Institute between 2005 and 2012. Of the eligible women approached, 397 agreed to participate. Eligible women were newly diagnosed with stage I, II, or IIIa breast cancer; were scheduled to receive chemotherapy plus anastrozole (n = 114) or anastrozole alone (n = 173); were postmenopausal; were 75 years old or younger; and were able to speak and read English with ≥8 years of education. Women who had a history of neurological illness or cancer, reported hospitalization for psychiatric illness within 2 years, or had evidence of metastases were excluded.

Age- and education-matched controls without breast cancer (n = 110) were recruited from the University Center for Social and Urban Research via random digit dialing, responses to a local ad, or referrals of friends by breast cancer participants. Controls met the same participation criteria. All participants provided written informed consent; the study protocol was approved by the institutional review board.

Design

With a prospective, observational cohort, repeated measure design, participants were evaluated after surgery but before they began chemotherapy (if applicable) and anastrozole and at 6-month intervals up to 18 months after they had begun anastrozole (Table 1). The 6-month assessment in the chemotherapy-anastrozole group occurred after chemotherapy and before anastrozole initiation. Controls were assessed at comparable time points. Demographic information was collected at the baseline, and treatment information was verified via the medical record.

Measures

Cognitive function was assessed with a standardized neuropsychological battery evaluating multiple cognitive domains. Cognitive tests were selected on the basis of their established sensitivity to cognitive changes in this

TABLE 2. Summary of Neuropsychological Tests and Outcome Variables

Domain	Test	Outcomes	Range
Attention	Digit Vigilance[15]	Time	0+
		Errors	0+
	CANTAB Rapid Visual Information Processing[16]	Total hits	0+
		A′	0-1
		Mean latency	0+
Learning and memory	CANTAB Paired Associates Learning[16]	Stages completed	0-10
		Errors	0+
	CANTAB Spatial Working Memory[16]	Strategy	8-56
		Errors	0+
	Rivermead Story: recall[17]	Immediate	0-21
		Delayed	0-21
	Rey Auditory Verbal Learning[18]	Number correct (total)	0-15
		Number correct (delay)	0-15
		Number correct (trial 6)	0-15
	Rey Complex Figure: immediate[19]	Number accurate elements	0-36
	Rey Complex Figure: delayed[19]	Number accurate elements	0-36
Executive function	CANTAB Stockings of Cambridge[16]	Mean initial thinking time (5 moves)	0+
		Mean subsequent thinking time (5 moves)	0+
		Number of problems solved	0+
	D-KEFS Verbal Fluency[20]	Number correct	0+
Mental flexibility	Trail Making Test B[21]	Time	0-240
	D-KEFS Color-Word Interference[20]	Inhibition (scaled score)	1-19
		Inhibition/switching (scaled score)	1-19
		Scaled scores 1 and 2	2-38
		Composition scaled score	1-19
Psychomotor efficiency	Grooved Pegboard[22]	Insertion time, dominant hand	0+
		Insertion time, nondominant hand	0+
	Digit Symbol Substitution[23]	Number correct	0-133
Visuospatial ability	Rey Complex Figure: copy[19]	Number of accurate elements	0-36

Abbreviations: CANTAB, Cambridge Neuropsychological Test Automated Battery; D-KEFS, Delis Kaplan Executive Function System.

population and on the basis of the availability of alternate equivalent versions used with the controls' scores to mitigate practice effects at follow-up testing.[14] The comprehensive battery was administered and scored by nurses trained by a licensed clinical neuropsychologist, and it comprised 13 measures, some yielding multiple scores (Table 2). Because of the number of cognitive variables, we applied a data reduction technique to decrease the risk of a type I error. Exploratory factor analysis with principal component extraction and orthogonal rotation was applied to the 29 scores derived from the measures to reduce dimensionality and cluster scores. Eight factors were derived, and they accounted for 71% of the total variance. Individual measures with the highest loadings were included in each factor. Measures had factor loadings > 0.400; the factors and scores composing each factor are listed in Table 3. We reversed the direction of some scores (timed, errors) so that higher mean scores indicated better cognitive performance. Cognitive factors were derived as means of the individual measures z score–transformed with respect to the controls' baseline values.

We also examined potential covariates of cognitive function, including age, and well-validated measures of estimated verbal intelligence (National Adult Reading Test–Revised[24]), depressive symptoms (Beck Depression Inventory II[25]), anxiety (Profile of Mood States tension/anxiety subscale[26]), and fatigue (Profile of Mood States fatigue/inertia subscale[26]). Age and estimated verbal intelligence were assessed at the baseline in all groups; depressive symptoms, anxiety, and fatigue were assessed at all study time points.

Statistical Analysis

Descriptive statistics were generated to characterize the groups and identify any data anomalies that may have invalidated planned analyses. Groups were compared on categorical descriptors with chi-square tests and on continuous characteristics with an analysis of variance.

We performed linear mixed effects modeling of the derived composite scores and adjusted for age and estimated verbal intelligence at baseline. Where we found significant group, time, or group-by-time effects, we examined differences between groups and changes over time and calculated effect sizes for significant differences. To control for multiple comparisons, we established a conservative significance level at $P < .01$. Because of the potential influence of practice effects, we applied a standard regression-based approach where applicable; data

TABLE 3. Differences in Factor and Individual Neuropsychological Scores Among Groups at Enrollment

Factors and Individual Tests	Chemotherapy Plus Anastrozole: 1 (n = 114 or 28.7%)	Anastrozole Alone: 2 (n = 173 or 43.6%)	Controls: 0 (n = 110 or 27.7%)	Statistics and Post Hoc Comparisons
Verbal memory	−0.21 (0.69)	−0.30 (0.67)	−0.11 (0.75)	$F(2,394) = 2.5$, $P = .085$
Rey AVLT: total	55.2 (8.14)	52.9 (8.10)	54.7 (9.52)	$F(2,394) = 2.9$, $P = .057$
Rey AVLT: interference	11.3 (2.71)	10.8 (2.82)	10.8 (3.00)	$F(2,394) = 1.2$, $P = .307$
Rey AVLT: delay	11.2 (2.80)	10.7 (2.88)	10.7 (3.05)	$F(2,394) = 0.9$, $P = .391$
Verbal Fluency Test: total	39.5 (11.91)	39.1 (11.48)	39.6 (11.50)	$F(2,392) = 0.1$, $P = .934$
Rivermead Story: immediate recall	7.2 (2.76)	7.4 (2.37)	8.4 (2.88)	$F(2,226) = 6.3$, $P = .002$; 1, 2 < 0
Rivermead Story: delayed recall	5.7 (2.81)	5.8 (2.35)	7.5 (2.82)	$F(2,225) = 16.0$, $P < .001$; 1, 2 < 0
Mental flexibility	0.16 (0.68)	0.08 (0.84)	20.1 (4.67)	$F(2,394) = 4.3$, $P = .015$; 0 < 1
Color Word Interference: scaled scores 1 and 2	22.7 (3.51)	21.8 (4.58)	10.2 (2.39)	$F(2,244) = 10.7$, $P < .001$; 0 < 1, 2
Color Word Interference: composition-scaled score	11.6 (1.78)	11.1 (2.33)	11.3 (2.34)	$F(2,244) = 12.1$, $P < .001$; 0 < 1, 2
Color Word Interference: inhibition/switching 4—norming method scaled score	11.4 (2.25)	11.2 (2.47)	10.7 (2.35)	$F(2,393) = 0.2$, $P = .811$
Color Word Interference: inhibition 3—norming method scaled score	10.8 (2.49)	11.1 (2.52)		$F(2,393) = 1.4$, $P = .258$
Psychomotor efficiency	−0.04 (0.85)	−0.22 (0.93)	−0.09 (0.86)	$F(2,394) = 1.7$, $P = .184$
Grooved Pegboard: nondominant hand time	91.0 (20.30)	93.7 (23.91)	91.8 (24.15)	$F(2,382) = 0.5$, $P = .597$
Grooved Pegboard: dominant hand time	79.0 (17.46)	83.9 (20.98)	80.7 (16.86)	$F(2,388) = 2.4$, $P = .093$
Digit Symbol Substitution	70.5 (14.03)	68.7 (12.98)	70.2 (12.85)	$F(2,394) = 0.8$, $P = .441$
Attention	−0.23 (1.01)	−0.22 (1.01)	−0.06 (0.88)	$F(2,388) = 1.1$, $P = .320$
Rapid Visual Information Processing: total hits	16.6 (4.53)	16.9 (4.89)	17.7 (4.59)	$F(2,388) = 1.5$, $P = .220$
Rapid Visual Information Processing: A′	0.90 (0.048)	0.90 (0.05)	0.91 (0.05)	$F(2,387) = 1.6$, $P = .202$
Rapid Visual Information Processing: mean latency	466.6 (125.53)	472.1 (108.95)	464.2 (93.37)	$F(2,387) = 0.2$, $P = .829$
Visual memory	0.14 (0.50)	0.01 (0.73)	−0.08 (0.91)	$F(2,235) = 3.0$, $P = .053$
CANTAB Paired Associates Learning: stages completed	4.9 (0.30)	4.9 (0.41)	4.8 (0.56)	$F(2,233) = 2.2$, $P = .116$
CANTAB Paired Associates Learning: errors adjusted	19.8 (14.05)	25.3 (21.90)	23.1 (24.99)	$F(2,238) = 3.5$, $P = .032$; no significant post hoc contrasts
Rey Complex Figure: copy	32.6 (2.79)	32.5 (3.10)	31.8 (3.06)	$F(2,394) = 2.3$, $P = .097$
Executive function	−0.33 (0.67)	−0.47 (0.61)	−0.07 (0.71)	$F(2,394) = 12.7$, $P < .001$; 1, 2 < 0
CANTAB Stockings of Cambridge: mean initial thinking time—5 moves	9899.5 (8461.51)	10,795.5 (8254.06)	15,322.7 (9697.61)	$F(2,393) = 12.8$, $P < .001$; 1, 2 < 0
CANTAB Stockings of Cambridge: problems solved, minimum moves	7.8 (1.93)	7.9 (1.76)	8.6 (1.75)	$F(2,394) = 6.29$, $P = .002$; 1, 2 < 0
CANTAB Spatial Working Memory: errors	37.3 (17.91)	43.4 (16.49)	37.1 (17.96)	$F(2,394) = 6.2$, $P = .002$; 2 > 0, 1
CANTAB Spatial Working Memory: strategy	34.7 (5.83)	36.7 (5.08)	34.4 (5.67)	$F(2,394) = 7.6$, $P = .001$; 2 > 0, 1
Visual working memory	0.06 (0.70)	−0.11 (0.85)	−0.08 (0.85)	$F(2,394) = 1.5$, $P = .222$
CANTAB Stockings of Cambridge: mean subsequent thinking time—5 moves	1857.6 (2059.06)	3172.7 (5290.80)	2749.1 (4270.86)	$F(2,230) = 5.4$, $P = .005$; 2 > 1
Rey Complex Figure: delayed recall	21.1 (6.19)	20.6 (5.80)	20.5 (6.49)	$F(2,392) = 0.4$, $P = .665$
Rey Complex Figure: immediate recall	22.0 (6.40)	21.5 (5.92)	21.6 (6.54)	$F(2,394) = 0.2$, $P = .795$
Concentration	−0.09 (0.80)	0.01 (0.90)	−0.003 (0.87)	$F(2,391) = 0.5$, $P = .617$
Digit Vigilance: time	177.9 (34.30)	177.1 (35.60)	174.3 (35.74)	$F(2,391) = 0.3$, $P = .712$
Digit Vigilance: errors	3.9 (4.62)	4.7 (5.09)	4.2 (4.41)	$F(2,391) = 0.8$, $P = .445$

Abbreviations: AVLT, Auditory Verbal Learning Test; CANTAB, Cambridge Neuropsychological Test Automated Battery.
The data are presented as means and standard deviations.

TABLE 4. Sample Characteristics at Enrollment (n = 397)

Characteristic	Chemotherapy Plus Anastrozole (n = 114)	Anastrozole Alone (n = 173)	Controls (n = 110)	*P*
Age, mean (SD), y	59.2 (5.5)	61.8 (6.5)	58.6 (6.1)	<.001
Education, mean (SD), y	14.8 (2.9)	14.9 (2.8)	14.9 (2.9)	.950
NART-R, mean (SD)	107.6 (9.2)	108.4 (8.7)	112.4 (9.1)	<.001
Race, No. (%)				.041
White	107 (93.9)	169 (97.7)	100 (90.9)	
Black	7 (6.1)	4 (2.3)	10 (9.1)	
Stage, No. (%)				<.001
I	45 (39.5)	149 (86.6)	NA	
IIa	38 (33.3)	19 (11.0)	NA	
IIb	19 (16.7)	4 (2.3)	NA	
IIIa	12 (10.5)	0 (0.0)	NA	
BDI-II, mean (SD)	6.6 (6.83)	5.2 (5.89)	5.6 (6.33)	.192
POMS tension/anxiety, mean (SD)	9.6 (6.21)	6.8 (5.10)	6.9 (6.10)	<.001
POMS fatigue/inertia, mean (SD)	5.7 (5.33)	5.5 (6.08)	5.6 (5.66)	.783

Abbreviations: BDI-II, Beck Depression Inventory II; NA, not applicable; NART-R, National Adult Reading–Revised; POMS, Profile of Mood States; SD, standard deviation.

from the controls were used to adjust for practice effects in the treatment groups.

RESULTS

Table 4 shows the sample characteristics at enrollment. The anastrozole-alone group was older ($P < .001$), and controls had higher estimated intelligence scores ($P < .001$). The chemotherapy-anastrozole group had a higher disease stage than the anastrozole-alone group ($P < .001$) and greater anxiety than both groups ($P < .001$).

Differences at enrollment in factor *z* scores and individual neuropsychological test scores are shown in Table 3. Before therapy, women with breast cancer performed worse than controls on measures of mental flexibility ($P < .01$). In contrast, women who received chemotherapy plus anastrozole had better executive function than controls ($P = .016$). The groups did not differ before therapy on the other cognitive factors.

Cognitive Function

Controlling for age and estimated intelligence, we found that the controls had better executive function than the anastrozole-alone group before therapy ($P = .001$, $d = .14$) and 6 ($P = .002$, $d = .12$), 12 ($P = .0001$, $d = .14$), and 18 months ($P < .0001$, $d = .16$) after therapy initiation (Fig. 2A-C). Similarly, there was a trend toward the controls performing better than the chemotherapy-anastrozole groups before chemotherapy ($P = .04$, $d = .08$) and at 6 months ($P = .09$, $d = .06$), and controls performed significantly better at 12 ($P = .005$, $d = .10$) and 18 months ($P = .001$, $d = .11$).

We also found significant group, ($P = .004$) time ($P < .0001$), and group-by-time effects ($P < .0001$) for visual working memory and significant group-by-time effects ($P = .0005$) for concentration. Both the anastrozole-alone and chemotherapy-anastrozole groups showed a pattern of decline during the first 6 months of anastrozole for these factors. We observed a decline in visual working memory in the first 6 months of therapy ($P = .0008$, $d = .15$) in the anastrozole-alone group; this was followed by an improvement from 6 to 12 months ($P < .0001$, $d = .45$) and another decline from 12 to 18 months ($P < .0001$, $d = .24$). After an initial improvement in visual working memory during chemotherapy, the chemotherapy-anastrozole group also displayed a deterioration during the first 6 months of anastrozole ($P < .0001$, $d = .26$), and this was followed by an improvement in function from 12 to 18 months ($P < .0001$, $d = .32$). The performance of the controls improved from 6 to 12 months ($P = .003$). Similarly, we observed a deterioration in concentration from the period before therapy to 6 months after therapy initiation in the anastrozole-alone group ($P = .0002$, $d = .17$), an improvement from 6 to 12 months ($P = .001$, $d = .15$), and a trend toward a decline from 12 to 18 months ($P = .02$, $d = .12$). In the chemotherapy-anastrozole group, we observed a deterioration in concentration during the first 6 months of anastrozole ($P < .0009$, $d = .15$) followed by an improvement from 12 to 18 months ($P = .008$, $d = .14$). No change in concentration was observed in controls.

There were also group differences for visual memory ($P = .002$); the controls performed more poorly than the chemotherapy-anastrozole groups before therapy ($P = .004$) and the anastrozole-alone and chemotherapy-anastrozole groups at 18 months, ($P = .001$ and

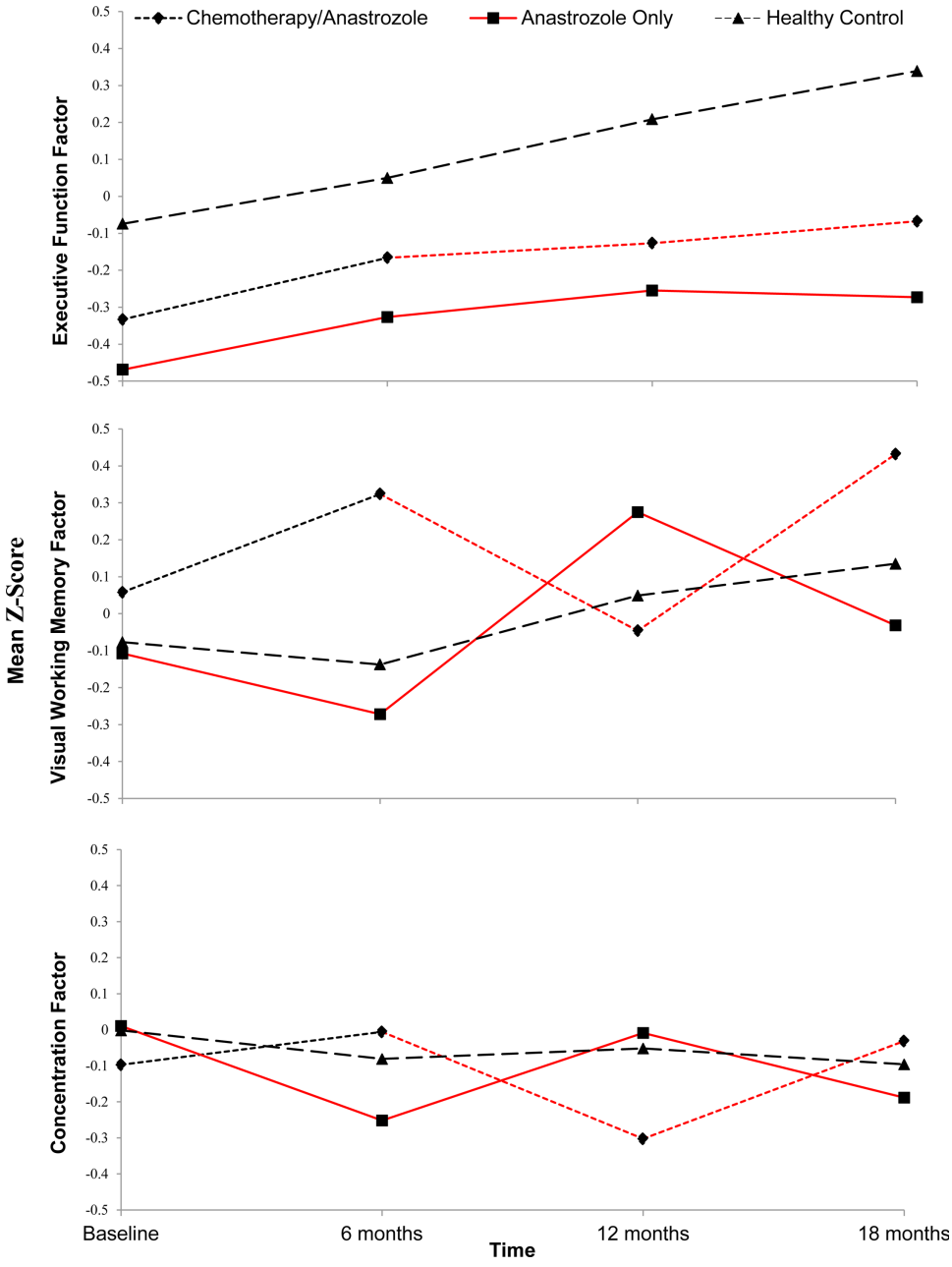

Figure 2. Group response profile: (A) executive function factor over 18 months, (B) visual working memory factor over 18 months, and (C) concentration factor over 18 months. The results for the anastrozole-alone group have been shifted for comparison because of the lack of a prechemotherapy assessment in that group. Red indicates exposure to anastrozole.

$P = .009$, respectively), and controls were poorer than the chemotherapy-anastrozole group at 12 months ($P = .002$). Similarly, there were group ($P < .0001$) and group-by-time effects ($P = .00006$) for mental flexibility, with the controls performing more poorly than the chemotherapy-anastrozole and anastrozole-alone groups before therapy ($P < .0001$ and $P = .0007$, respectively). There was also improved performance in verbal memory and psychomotor efficiency for all groups, and this likely demonstrated practice effects.

DISCUSSION

In this first large cohort study to comprehensively assess cognitive function over 18 months, we found that in comparison with controls, women who received anastrozole alone or chemotherapy plus anastrozole had significantly

poorer executive function from the period before therapy through the first 18 months of treatment. We also found a consistent pattern of changes in visual working memory and concentration with therapy.

Poorer Executive Function

Women in both breast cancer groups had poorer executive functioning before and during therapy that did not appear to be influenced by treatment. Multiple mechanisms, including changes in inflammatory cytokines, neurotransmitter dysregulation, stress, and mood, may explain this persistently poorer executive functioning.[27] We found depressive symptoms to be related to executive function over time, but this relationship did not substantively change the pattern of results. Executive functioning is critical for planning, organizing, and decision making, and impairment of this domain can have a deleterious effect on one's ability to perform effectively at work and socially.

Before Chemotherapy to the Pre-Anastrozole Assessment

Before chemotherapy, women with breast cancer who received chemotherapy had a trend toward better visual working memory in comparison with controls, and their performance improved at the pre-anastrozole assessment; this suggested practice effects. There was no change in the controls on this factor.

Pre-Anastrozole Assessment to 6 Months After Anastrozole Initiation

There was a significant deterioration in visual working memory and concentration in both the chemotherapy-anastrozole and anastrozole-alone groups with the first 6 months of anastrozole. In comparison with controls, women who received chemotherapy plus anastrozole had a trend toward poorer performance 6 months after anastrozole initiation. Controls had no change in performance in these factors. Reductions in reproductive hormones that occur with AIs may explain this initial decline in performance in both treatment groups.

Six to 12 Months After Anastrozole Initiation

Paradoxically, the deterioration in visual working memory and concentration that occurred with the initial 6 months of anastrozole was followed by improved performance in these domains at 12 months. In comparison with controls, women in the chemotherapy-anastrozole and anastrozole-alone groups performed better 12 months after anastrozole initiation. It is not clear why women with breast cancer have improved performance in these domains during this interval. Their reproductive hormone levels likely remain low with continued therapy. This may reflect compensation for the cognitive changes initially experienced.

We explored whether cognitive reserve contributed to this improvement. Cognitive reserve theory postulates that intelligence, education, mental activity, and social engagement mitigate or compensate for cognitive deterioration.[28,29] In our study, higher estimated verbal intelligence was highly significantly correlated with better cognitive function in all domains. Therefore, we explored whether cognitive reserve, assessed via estimated verbal intelligence (National Adult Reading–Revised scores classified as IQ $\leq$ 110 or $>$ 110), explained this pattern. We found that the National Adult Reading–Revised classification moderated the group-by-time effect for visual working memory ($P = .05$) but not concentration, so the performance of women receiving anastrozole alone with a higher estimated intelligence had better working memory than those with a lower estimated intelligence ($P = .05$). Therefore, greater cognitive reserve may partially explain the improvement observed with respect to visual working memory.

Twelve to 18 Months After Anastrozole Initiation

However, from 12 to 18 months, the anastrozole-alone group again exhibited a decline in working memory and a trend toward a deterioration in concentration. If cognitive reserve theory provides a plausible explanation for the improvement in working memory and concentration observed from 6 to 12 months, the deterioration in working memory at 18 months suggests that the ability of variables such as intelligence and education to mitigate the effects of therapy on cognitive function diminishes over time. Another plausible mechanism for these later cognitive declines may be that the additive effect of chronic stress associated with the cancer diagnosis and treatment results in changes in the prefrontal regions.[30] The affected domains suggest a central neurotoxicity with some specificity to the prefrontal cortices and hippocampus, and this is supported by imaging studies.[31,32] Initial exposure to anastrozole and the secondary hypoestrogenism might reduce brain metabolism[33,34] and synaptic connectivity[35,36] and lead to cognitive decline.[37] Hypocortisolemia from stress also might independently reduce brain metabolism and synaptic density. Thus, the combination of stress and hypoestrogenism may compromise cognitive function in domains such as working memory and concentration.[38] Initially, the brain may have sufficient reserves to be able to generate new cognitive strategies, but

with persistent hypoestrogenism, with or without stress, even alternative neural pathways may be compromised.[39]

To explore this possibility, we controlled for depression, anxiety, and fatigue over time in the mixed effects modeling and found that higher anxiety was related to poorer visual working memory ($P = .04$). On the basis of this finding, we compared anxiety scores between groups and explored changes over time, and we found a group-by-time interaction for the chemotherapy-anastrozole group; this indicated that these women had significantly more anxiety at the baseline, improved to show no differences from the other groups at 6 months, and then became more anxious than the other groups from 12 to 18 months. No differences in anxiety were found between the anastrozole-alone and control groups, with anxiety scores generally decreasing over 18 months. These results point to an association between anxiety and visual working memory for women who received chemotherapy plus anastrozole, but they do not fully explain the trajectory of this cognitive factor. Neither depressive symptoms nor fatigue was consistently associated with the cognitive function factors at any time point. Although these results lend some support to the relationship between chronic stress and the deterioration in cognitive function in women receiving adjuvant therapy, they do not fully explain our results. It is important to keep in mind that a measure of anxiety (Profile of Mood States tension/anxiety subscale) may not be an optimal surrogate of chronic stress. Ultimately, these results point to a need for further exploration of this potential mechanism with more sensitive approaches to the assessment of stress, including the use of biomarkers and neuroimaging techniques.

Studies of cognitive function with ET in breast cancer have yielded conflicting results. Tamoxifen has been associated with deteriorations in visual and verbal memory, verbal ability, processing speed, and visuospatial ability.[7,40-42] The evidence for cognitive changes with AIs is less clear, in part because few studies have examined cognitive function exclusively with AIs. Moreover, methodological concerns and differences hinder efforts to compare results across studies. Samples in some earlier studies were heterogeneous and combined premenopausal women and postmenopausal women[3,10,11,41] and women who received AIs and women who received tamoxifen.[8,10,42,43] Several studies had small samples[3,8,40-42,44] and lacked control groups, which are essential for the comparison and isolation of the influence of practice effects.[3,10,11,45]

Different approaches to cognitive assessment may explain the contradictory results. Some studies employed cognitive screening: they provided information about global cognitive changes but failed to detect subtle changes more commonly experienced or to identify changes in specific cognitive domains.[1] Other studies relied on self-reporting of cognitive problems[6,46] or used measures that were initially developed to assess gross cognitive disorders in patients with stroke, neurotrauma, or dementia.[3,7,10,11,47] We included measures from the Cambridge Neuropsychological Test Automated Battery,[16] a computerized battery composed of challenging cognitive tasks that may be more sensitive to these subtle changes. Importantly, several earlier studies employed a cross-sectional design,[4,40-42,44,45] and in some longitudinal studies, no true pretherapy assessment was made because many participants had already begun ET therapy at the baseline[3,8,11,48] or received chemotherapy before the initial cognitive assessment.[10] With these designs, it is not possible to discern whether cognitive impairments existed before therapy or whether there were cognitive changes with AI therapy. Our results indicate that women with breast cancer have poorer executive function before they begin therapy, and this demonstrates the importance of longitudinal designs that include assessments before the initiation of any systemic therapy, including chemotherapy.

Finally, conflicting results across longitudinal studies may reflect differences in the timing of follow-up assessments.[7,10] Our study is the first to report assessments at 6-month intervals up to 18 months after the initiation of ET.

With the exception of the poorer executive function for the anastrozole-alone group versus controls before AI initiation ($d = 0.61$), most effect sizes for differences between patients and controls were small to medium (ie, $d < 0.4$). Studies using objective neuropsychological tests have shown subtle cognitive declines during AI therapy. These effects may reflect the level of sensitivity of some study measures to subtle cognitive changes experienced by women with breast cancer.[49,50] These subtle cognitive changes may decrease women's ability to perform in cognitively challenging situations.[51]

Although the cohorts differed in age, estimated intelligence, and anxiety before therapy, these differences were likely not clinically meaningful. Furthermore, we controlled for age and intelligence in our analysis, and the level of anxiety in the chemotherapy-anastrozole group (mean, 9.8) was within the normative value for adult women (mean, 9.2).[26]

The strengths of this study include the longitudinal design, the inclusion of a pretherapy assessment, and the ability to examine the potential additive influence of

chemotherapy on the effects of AIs on cognitive function. The study is limited by a sample predominantly composed of white, well-educated women, and this limits generalizability.

Additional research is needed to examine cognitive function across the entire trajectory of AI therapy and to determine whether cognitive function improves after treatment completion. Interventions to attenuate cognitive decline are also needed. Physical activity interventions may be of particular benefit because they are associated with improved working memory, executive function, and psychomotor efficiency in older adults, the very cognitive domains that deteriorate with adjuvant therapy use in breast cancer.[52]

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CONFLICT OF INTEREST DISCLOSURES

Sarah Berga reports serving on a scientific advisory board for Pfizer. Christopher Ryan reports personal fees from Novo Nordisk for his work as a consultant on a study on diabetes.

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