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Cognitive function in postmenopausal breast cancer patients one year after completing adjuvant endocrine therapy with letrozole and/or tamoxifen in the BIG 1-98 trial

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Abstract

Endocrine therapy for breast cancer may affect cognition. The purpose of this study was to examine whether cognitive function improves after cessation of adjuvant endocrine therapy. Change in cognitive function was assessed in 100 postmenopausal breast cancer patients in the BIG 1-98 trial, who were randomized to receive 5 years of adjuvant tamoxifen or letrozole alone or in sequence. Cognitive function was evaluated by computerized tests during the fifth year of trial treatment (Y5) and 1 year after treatment completion (Y6). Cognitive test scores were standardized according to age-specific norms and the change assessed using the Wilcoxon signed-rank test. There was significant improvement in the composite cognitive function score from Y5 to Y6 (median of change = 0.22, effect size = 0.53, $P < 0.0001$). This improvement was consistent in women taking either tamoxifen or letrozole at Y5 ($P = 0.0006$ and $P = 0.0002$, respectively). For postmenopausal patients who received either adjuvant letrozole or tamoxifen alone or in sequence, cognitive function improved after cessation of treatment.

Keywords

Cognitive function; Breast cancer; Aromatase inhibitor; Tamoxifen; Letrozole; Quality of life

Introduction

Most postmenopausal early stage breast cancer patients have hormone receptor-positive disease and are, therefore, treated with endocrine therapy [1]. Several studies suggest that adjuvant endocrine therapy is associated with impaired cognitive function during treatment [2–5], and that tamoxifen may have a more adverse effect than aromatase inhibitors [2,6,7]. No published study has specifically evaluated the trajectory of cognitive function after ceasing adjuvant endocrine therapy. We evaluated the change in cognitive function 1 year after cessation of adjuvant endocrine therapy in a subgroup of postmenopausal early-stage breast cancer patients treated in the BIG 1-98 trial.

Methods

The BIG 1-98 trial (March 1998–May 2003) randomized 8010 postmenopausal women with hormone receptor-positive tumors to receive one of four adjuvant endocrine therapy options after stratification by institution and chemotherapy (Fig. 1) [8,9]. A substudy assessed cognitive function at Y5 (during the fifth year on endocrine therapy) and Y6 (approximately

1 year after cessation of therapy). Cross-sectional Y5 data, showing that patients on letrozole had better overall cognitive function than those on tamoxifen, have been previously reported [6]. We now report longitudinal data assessing cognitive changes between Y5 and Y6. The substudy protocol was approved by the local and International Breast Cancer Study Group (IBCSG) ethics committees and the required health authorities of each participating center. All the patients gave informed consent to participate in the substudy and parent study.

Objective cognitive function was assessed using a brief computerized test battery (CogState Ltd; http://www.cogstate.com) which is free from practice effects [10–13]. Details of the test battery are given in Table 1. A composite score, representing the average standardized score of each task for each individual, was prospectively defined as the primary endpoint.

Scores for each task were transformed, then standardized according to age-specific norms (*Z*-scores) [14]. A positive *Z*-score indicates a patient performed better than average for her age group. The composite score was calculated by the mean of the *Z*-scores for all tasks. For five patients who were missing data on some individual tasks, the mean of the scores of the completed tasks was taken as their composite score. A positive difference in the composite score from Y5 to Y6 indicates that cognitive function improved.

Change in cognitive function from Y5 to Y6 was assessed using the Wilcoxon signed-rank test, first for all the patients and then separately for each treatment group. No substantial normality violations were noted. The effect of endocrine treatment on change in cognitive function was assessed using two-way ANOVA controlling for the effect of language. Descriptive statistics of change in performance (mean, SD, and effect size) were calculated per treatment group for each task. Effect size is defined as the difference between Y6 and Y5 measurements divided by the standard deviation of the difference.

The effect of treatment on the changes in cognitive function was also assessed nonparametrically using the stratified Wilcoxon Rank Sum test (adjusted for language). To account for potential imbalances between treatment groups, a linear model was created for the CogState composite score to further evaluate the treatment effect using a stepwise selection procedure with the following covariates: treatment, language, age, chemotherapy received, tumor size, history of depression, treatment for depression at Y5, time between assessments, and ECOG performance status at Y5. Treatment and language were forced into the model. Comparisons of scores between the two monotherapy arms, and between monotherapy and sequential therapy arms for tamoxifen and for letrozole, respectively, were based on two-way ANOVA controlling for language. All *P* values were based on two-sided tests. A *P* value <0.05 indicates statistical significance.

Of the 135 patients recruited to this substudy, 35 were ineligible for this analysis (Fig. 1), leaving 100 patients as eligible for inclusion. The Y6 assessment was undertaken a median of 365.5 days (range 191–699 days) after ceasing protocol endocrine therapy.

Results

There was significant improvement in cognition, as measured by the change in composite score, from Y5 to Y6 (median of change = 0.22, effect size = 0.53, $P < 0.0001$) (Fig. 2, Table 2). This finding was consistent in women taking either tamoxifen or letrozole at Y5 (median of change = 0.20, effect size = 0.54, and $P = 0.0006$; or median of change = 0.23, effect size = 0.53, and P = 0.0002, respectively) and across all cognitive tasks (though not statistically significant for the learning task) (Table 2). The effect size, defined as the difference in score between Y5 and Y6 divided by the standard deviation of the difference, was small for the individual tasks (range 0.17–0.35) and moderate for the change in overall cognition as measured by the composite score (0.53). After adjusting for language and any

significant covariates, the change in cognitive function (Y6–Y5) of patients taking letrozole at Y5 was not different from those taking tamoxifen at Y5. Exploratory analyses revealed no differences in the change in cognitive function (Y6–Y5) between the monotherapy arms or the monotherapy versus sequential arms.

Discussion

In this substudy, cognitive function was better approximately 1 year after cessation of adjuvant endocrine therapy as compared with the fifth year on therapy. For the composite score, this improvement (effect size = 0.53) was, by convention, moderate in magnitude. Changes in cognitive function of a similar magnitude have been observed in healthy adults given methylphenidate for cognitive enhancement [15,16]. In addition, stressing the clinical relevance of our findings, the effect size observed is larger than that required by the FDA for approval of drugs that enhance cognition in diseases such as schizophrenia [17]. Although there was no untreated control group in the randomized BIG 1-98 trial, the improvement is not thought to be because of practice effects as these do not operate in the CogState test battery, and the magnitude of improvement is too large. Cognitive function was not assessed before starting endocrine therapy, and so we cannot calculate how cognition 1 year after cessation of therapy compares with baseline cognitive function before commencing adjuvant endocrine therapy. Nevertheless, this study suggests that if adjuvant endocrine therapy affects cognition in postmenopausal women, that effect is at least partly reversible with cessation of therapy, which is a relevant and new finding for postmenopausal women with hormone receptor positive breast cancer.

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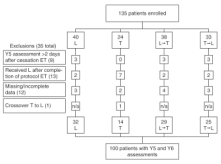

Fig. 1.

CONSORT diagram of the BIG 1-98 Cognitive Function Substudy. *T* tamoxifen for 5 years, *L* letrozole for 5 years, *T* → *L* tamoxifen for 2 years followed by letrozole for three years, *L* → *T* letrozole for 2 years followed by tamoxifen for 3 years, *ET* endocrine therapy, *Y5* cognitive function assessment taken at the end of 5 years of ET, *Y6* cognitive function assessment taken approximately 1 year after completion of ET

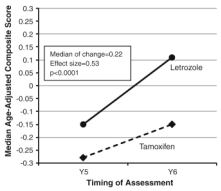

Fig. 2.

Change in median age-adjusted composite score from the assessment taken at the end of endocrine therapy (*Y5*) to the assessment taken approximately 1 year after completion of endocrine therapy (*Y6*) according to endocrine therapy received, showing significant improvement in cognition, as measured by the composite score, from *Y5* to *Y6*

Table 1

Cogstate cognitive function test battery

Task	Verbal/ non-verbal	Cognitive domain	Outcome measured
Detection	Non-verbal	Speed of psychomotor function	Performance speed
Identification and monitoring	Non-verbal	Visual attention	Performance speed
Learning	Non-verbal	Visual learning and memory	Performance accuracy
Memory	Non-verbal	Attention and working memory	Performance accuracy
Shopping list[a]	Verbal	Verbal learning and memory	Number of correct responses
Shopping list delayed recall[a]	Verbal	Verbal learning and memory	Number of correct responses

[a]Subjects were required to learn a 12-item shopping list and recall it after 20 min

Table 2

Descriptive statistics of cogstate battery assessment by timepoint and change in score

Task	Y5 (during the fifth year on ET)				Y6 (approximately 1 year after ceasing ET)				Change (Y5–Y6)						*P*
	n	Med	Min	Max	*n*	Med	Min	Max	Mean	Med	SD	Min	Max	Effect Size	
Detection	100	0.00	−3.13	1.65	100	0.36	−2.43	1.79	0.14	0.11	0.68	−1.69	2.96	0.21	0.05
Identification	99	0.42	−2.59	3.01	100	0.51	−1.69	3.13	0.17	0.11	0.61	−1.29	2.17	0.28	0.008
Learning	100	−0.98	−4.43	1.18	100	−0.79	−4.05	1.61	0.20	0.17	1.19	−3.74	3.66	0.17	0.09
Memory	100	0.15	−11.0	4.02	100	0.41	−5.50	4.02	0.76	0.55	2.18	−6.2	6.48	0.35	0.0002
Monitoring	100	−0.68	−3.18	1.82	100	−0.62	−3.52	2.30	0.18	0.14	0.78	−2.43	2.57	0.23	0.009
ISLT	99	−0.35	−3.84	1.74	100	−0.22	−3.37	1.51	0.23	0.23	0.98	−2.09	2.79	0.23	0.03
Delayed ISLT	98	−0.03	−3.78	1.22	98	0.11	−2.67	1.22	0.17	0.00	0.82	−1.67	2.22	0.21	0.04
Composite	100	−0.20	−2.85	1.33	100	0.06	−2.17	1.19	0.26	0.22	0.49	−0.81	1.74	0.53	<0.0001

ET endocrine therapy, *ISLT* International shopping list test, *n* number, *med* median, *min* minimum, *max* maximum, *SD* standard deviation

Measures of performance speed were normalized using logarithmic base ten transformation. Measures of performance accuracy (%) were normalised using arcsine transformation. The primary endpoint was the composite score calculated from all seven tasks