Study of Neurobehavioral Symptoms and Impairments in Breast Cancer Patients Receiving Adjuvant Aromatase Inhibitor Therapy

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INTRODUCTION

Adjuvant chemotherapy and hormone therapy for breast cancer has significantly improved survival in women with early stage breast cancer and reduced the rate of recurrence of the disease. Unfortunately**, there are concerns that adjuvant breast cancer treatment may be associated with impaired cognitive functioning**, the so-called "chemobrain" or "chemofog" effect . Patients have reported difficulty with concentration, impaired verbal and visual memory, problems organizing information, and word-finding difficulties. These complaints have translated into quality of life issues for these patients, along with fears as to the possible side effects of adjuvant chemotherapy treatment.

Most studies of treatment-associated cognitive dysfunction have been reported following treatment with adjuvant chemotherapy, but there may also be effects of endocrine treatment for breast cancer, although these have been less well studied (Minisinski et al., 2004). Because of the accumulating knowledge regarding the importance of estrogen for cognitive functioning, there is growing concern about adjuvant hormonal therapy for breast cancer. Estrogen receptors have been identified in several areas of the brain important in cognitive performance, including the prefrontal cortex, hippocampus, and amygdala (Jenkins et al., 2007).

Many women taking tamoxifen have complained of cognitive dysfunction, but the results of prospective studies regarding aromatase inhibitors and cognitive impairment have been mixed. Several studies have examined the effects of anastrozole compared to tamoxifen. Results show women taking anastrozole or tamoxifen were equally likely to show cognitive decline as compared to normal controls (Collins et al., 2009). However, a second study found that women who received anastrozole had poorer verbal and visual learning and memory than women who received tamoxifen (Bender et al., 2007). Similar results were found in a pilot study involving women who participated in the adjuvant trial of anastrozole vs. tamoxifen vs. a combination of the two (ATAC). Findings suggested that anastrozole may induce cognitive dysfunction (Jenkins et al., 2003).

Similar results have been found in studies examining exemestane and impaired cognitive functioning. Shilder and collegues (2009) studied women receiving doxorubicin/cyclophosphamide chemotherapy and exemestane or tamoxifen. Memory complaints were reported by 28% of AC/tamoxifen users compared to 24% of AC/exemestane. Significant differences were found between tamoxifen and exemestane users, with exemestane related to slower manual motor speed and tamoxifen related to worse verbal functioning. Both groups were poor on verbal fluency and information processing speed.

Given these varied findings and the relative lack of published studies examining aromatase inhibitors in cognitive functioning**, the question of whether there are cognitive problems following specific adjuvant therapies (i.e. aromatase inhibitors) for breast cancer remains important.**

AIMS

We initiated a prospective clinical trial to compare baseline and 1-year change in neurophysiological testing in women initiating adjuvant aromatase inhibitor (AI) treatment with two goals in mind:

- **To determine whether treatment with AI may be associated with the development of cognitive or other mental impairments.**

- **To determine the most appropriate subjective and/or objective measures of changes in cognitive and mental status**, both for this particular type of study and potentially also for general clinical use. In particular:
  - To examine how subjective and objective measures may interrelate in this population.
  - To determine if a shortened neuropsychological battery has adequate reliability, sensitivity and specificity to be useful for (a) research and/or (b) clinical assessments of the relevant functions.

METHODS/ RESULTS

Participants

Women with a hormone receptor-positive stage 0-III breast cancer who were about to begin adjuvant AI treatment were eligible for enrollment. We compared intra-individual neurophysiological testing results at baseline (Session I) and following one year of AI treatment (Session II).

	Session I (M±SD)	Session II (M±SD)
N	60	38
Age (years)	58.88± 8.13	60.13 ± 7.80
Education (years)	16.47 ± 2.76	17.00 ± 2.16

Subjective measures of cognitive status

Domain Assessed	Subjective Questionnaire
Activities of Daily Life	Cognitive Problems in Daily Life
Social & Economic Resources, Mental & Physical Health	Functional Assessment Questionnaire
Memory Complaints	Squire Memory Questionnaire
Fatigue	Fatigue Symptom Inventory
Depression	Center for Epidemiological Studies Depression Scale (CES-D)
Mood Reactions to Life Situation	Profile of Mood States – short form

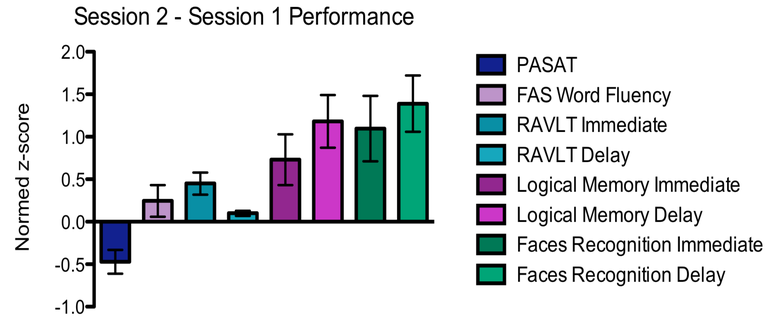
These subjective questionnaires were chosen to assess how the women evaluated their own cognitive and emotional well-being. Women rated themselves within the normal range on all measures. However, **there was an increase in depression (as measured by the CES Depression Scale) from the beginning of AI treatment (8.4) to follow-up one year later (11.4).**

Objective measures of cognitive status

Neurophysiological Domain	Standardized Assessment
General Intelligence	Wechsler Adult Intelligence Scale
Attention	Paced Auditory Serial Addition Task (PASAT) Trail Making Test A & B Controlled Performance Task
Perceptual-Motor Performance	Symbol Digits Modalities Test (SDMT) Grooved Pegboard
Visual Long-term Memory	Rey Complex Figure Test (RCFT) Wechsler Memory Face Recognition
Verbal Long-term Memory	Rey Auditory Verbal Learning Test (RAVLT) Wechsler Memory Logical Memory Test
Language	Category Fluency (Animals) Word Fluency (FAS)
Executive Functioning	Booklet Category Test (BCT) Wisconsin Card Sorting Test (WCST)
Working Memory	Digit Span & Digit Symbol

The measures were chosen for several reasons: (a) They have been suggested to show sensitivity to dysfunction due to treatment in breast cancer patients, and/or (b) they are sensitive and reliable measures of dysfunction in domains that may be related to the effects of breast cancer treatment,.

Objective performance difference following one-year of AI treatment (n=38)



Data from each measure were transformed into z-scores to accommodate comparisons between measures. A z-score has a mean of zero and a standard deviation of one. Comparison of z-score performance between sessions 1 and 2 revealed statistically significant differences (with the significance level set at p=0.05, test-wise).

Women demonstrated impairment from Session I to Session II only on the PASAT (a measure of attention) on the PASAT Trial I (p=0.030). They showed improvement from Session I to Session II on the following tests: FAS Total (p=.014), RAVLT 5-1 (p=.028), RAVLT % (p=.021), Logical Memory I (p=.002) and II (p<.001), Faces I & II (p<.001 for both).

CONCLUSIONS/FUTURE DIRECTIONS

We are still in the process of collecting data for Session II and are cautious in drawing firm conclusions here. However, thus far**, these data indicate that taking AI for one year does not have a detrimental effect on cognition**. Once the full dataset is complete, we can examine the group in more detail, looking at the following relationships:

1. Is there a subgroup of women who exhibit impairments that are not revealed when looking at the group as a whole? Other studies have indicated that this might be the case.
2. Is there an effect of the type of AI treatment (anastrozole, letrozole, or exemestane) on cognition?
3. Is there any relationship between subjective measures of cognitive and emotional status and objective cognitive performance?
4. Are there differences between those women who have had chemotherapy and/or radiation treatment prior to AI treatment?

With the full dataset, we can begin to examine the above questions and others to gain a better understanding the effect of AI treatment on cognition.

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