Original Study

The Effect of Aromatase Inhibition on the Cognitive Function of Older Patients With Breast Cancer

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Abstract

This study examined the association between aromatase inhibitor (AI) therapy and cognitive function in older patients with breast cancer and evaluated the effects of AI therapy on cerebral metabolic activity, using positron emission tomography (PET) scans of the brain. Although no worsening of cognition was seen among the patients receiving AI therapy, changes in cerebral metabolic activity were observed. To the authors' knowledge, this is the first study to use PET scans to evaluate cognition in older patients with breast cancer receiving AI therapy.

Introduction: This study evaluated the association between aromatase inhibitor (AI) therapy and cognitive function (over a 6-month period) in a cohort of patients aged ≥ 60 years compared with an age-matched healthy control group, and it evaluated changes in regional cerebral metabolism as measured by positron emission tomography (PET) scans of the brain done in a subset of the patient cohort. **Patients and Methods:** Thirty-five patients (32 evaluable) and 35 healthy controls were recruited to this study. Patients with breast cancer completed a neuropsychological battery, self-reported memory questionnaire, and geriatric assessment before initiation of AI therapy and again 6 months later. Age-matched healthy control participants completed the same assessments at the same time points as the patient group. **Results:** No significant decline in cognitive function was seen among individuals receiving an AI from pre-treatment to 6 months later compared with healthy controls. In the PET cohort over the same period, both standardized volume of interest and statistical parametric mapping analyses detected specific changes in metabolic activity between baseline and follow-up uniquely in the AI patients, most significantly in the medial temporal lobes. **Conclusion:** Although patients undergoing AI treatment had few changes in neuropsychological performance compared with healthy controls over a 6-month period, regionally specific changes in cerebral metabolic activity were identified during this interval in the patient group. Additional longitudinal follow-up is needed to understand the potential clinical implications of these findings.

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Introduction

A growing body of literature has evaluated the potential effect of breast cancer therapy on cognitive function. However, there are limited data on the association between endocrine therapy and cognition, and despite the fact that breast cancer is a disease associated with aging, most studies have been performed with relatively young adults, so the effect of endocrine therapy for breast cancer on the cognition of older adults remains unknown.

Aromatase inhibitors (AIs), which are a mainstay of therapy for hormone receptor–positive, early-stage breast cancer in postmenopausal women, inhibit the enzyme aromatase, which leads to

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a reduction in estrogen levels throughout the body. Given that estrogen receptors are spread throughout the brain and that studies have found that estrogen promotes neuron growth and provides neuroprotective activity in vitro, there is a biologic reason to question whether aromatase inhibition might influence cognitive function.[1-3]

Conflicting data from randomized controlled studies exist concerning the effects of both estrogen replacement and estrogen deprivation on cognitive function in the clinical setting.[4-8] Likewise, clinical studies examining the effects of endocrine therapy on cognitive function of patients with breast cancer have produced inconsistent results, with some,[9-12] but not all,[13] suggesting a decline in cognitive function resulting from treatment.

The biologic basis of cognitive change as a result of cancer therapies is poorly understood. Previously, Silverman et al[14] found that treatment-related regional changes in brain metabolism are associated with changes in neuropsychological performance. For example, diminished metabolism in the posterior inferior frontal gyrus in the vicinity of Broca's area was specifically associated with diminished performance on a neuropsychological test of short-term memory in patients with breast cancer who had received adjuvant therapy.

This study sought to use neuropsychological testing to examine the association between AI therapy and cognitive function in a cohort of patients aged $\geq$ 60 years compared with an age-matched healthy control group and to evaluate changes in regional cerebral metabolism as measured by positron emission tomography (PET) scans of the brain performed for a subset of the patient cohort. The authors hypothesized that there would not be short-term changes in cognitive function among patients taking an AI compared with an age-matched healthy control group; however, regional changes in brain metabolism on PET imaging may be seen.

Materials and Methods

Study Population

Thirty-five patients (32 evaluable) and 35 healthy controls were recruited to the study. Patients aged $\geq$ 60 years with hormone receptor−positive stage I to stage III breast cancer who were about to receive adjuvant AI therapy as systemic therapy for breast cancer were eligible for the study and were recruited from the outpatient practice at City of Hope National Medical Center. These patients had received surgical therapy for their breast cancer and chemotherapy (if indicated). An age-matched healthy control group, solicited through the services of Marketing Systems Group, was recruited to participate in the study to enable comparison with the patients receiving AI therapy. Three patients who missed follow-up assessments were excluded from analysis. The study was approved by the institutional review board, and all study participants provided written, informed consent.

Patients were deemed ineligible if they had received estrogen replacement therapy within the past year or previous radiation treatment of the central nervous system. Other eligibility criteria included literacy in English, because many of the study measures were not validated in other languages.

Study Procedure

Study participants with breast cancer completed a neuropsychological battery, a self-reported memory questionnaire, and a geriatric assessment before initiation of AI therapy as well as 6 months later. Age-matched study participants in the healthy control group completed the same assessments at the same time points as the patient group.

The neuropsychological battery consisted of 13 standardized tests of neuropsychological function across 7 domains: attention; verbal memory; visual memory; and verbal, spatial, psychomotor, and executive functions (Table 1). The tests were chosen for succinctness, reliability, validity, and past use to enable comparison with normative data. This battery was previously tested in a study of older patients with breast cancer.[15]

The patients' self-reported assessment of their cognitive function was collected through the Squire Memory Self-Rating Questionnaire.[16] The questionnaire contains 18 items of self-reported cognitive function rated on a scale from −4 to +4. Three of the questions were found to have ambiguous loadings and were excluded from analysis, consistent with methodology used in a previously reported study.[16] The participants also completed a geriatric assessment including validated measures of functional status, comorbid medical conditions, psychological state, social support, nutritional status, cognitive function, and medications.[17,18]

Ten patients and 10 healthy controls completed a PET scan at both time points to assess changes in regional cerebral metabolism. Fluorine-18 fluorodeoxyglucose was used as the tracer. At each time point, 5 millicuries of tracer were administered intravenously. After a 40-minute period of tracer uptake in a dimly lit, quiet room, emission data were acquired for 30 minutes with a dedicated PET scanner (HR+; Siemens/CTI). Images were attenuation-corrected with emission data obtained from an external positron-emitting source and were summed over the acquisition period to yield a 3-dimensional representation of the regional distribution of resting metabolism.[19]

Statistical Analysis

Using independent-samples t tests and χ^2 tests, 32 patients receiving adjuvant AI therapy were compared with 35 healthy controls by baseline demographic characteristics as well as the functional domains that constitute the geriatric assessment battery. The longitudinal analysis evaluated the change in neuropsychological performance between baseline and 6-month follow-up using paired t tests. Standard scoring of neuropsychological tasks was based on population norms and adjusted for age, sex, and, in some cases, education. Comparisons between patients and their healthy counterparts were performed at baseline using independent-samples t tests. To control for the practice effects associated with repeated cognitive testing and to assess the clinical significance of changes in neuropsychological function, the degree of longitudinal change observed in patients was compared with that observed in controls using a t test.

Before analysis, PET images were reoriented into standardized space, spatially smoothed (full width at half maximum, 8 mm), and normalized to mean whole-brain metabolic activity. As previously described,[19,20] data were analyzed by (1) a standardized volume of interest (sVOI) approach using NeuroQ software (Syntermed, Inc, Atlanta, GA) and (2) a voxel-based statistical parametric mapping (SPM) method using SPM8 software generously provided by the Wellcome Trust Centre for Neuroimaging (London). To statistically protect for multiple comparisons, regions identified by SPM were noted only when containing voxels with significance of $P < .0005$, and the sVOI approach was used for methodologically