

Cognitive functioning during long-term tamoxifen treatment in postmenopausal women with breast cancer

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Abstract

Objective: Endocrine therapy is widely used—often for many years—in women with breast cancer. Yet little is known about cognitive functioning after long-term use of tamoxifen. We examine cognitive sequelae, approximately 3 years after diagnosis, in postmenopausal women with breast cancer who were treated with adjuvant tamoxifen.

Methods: Data from participants who underwent surgical operation with or without radiotherapy, participants who received adjuvant tamoxifen, and healthy controls were collected. Neuropsychological tests were administered, and participants completed questionnaires on health-related quality of life (Quality of Life Questionnaire Core 30 and Breast Cancer–Specific Quality-of-Life Questionnaire), menopausal symptoms (Functional Assessment of Cancer Therapy—Breast endocrine symptom subscale), and anxiety and depression (Hopkins Symptom Checklist).

Results: In total, 107 women participated (adjuvant tamoxifen group, $n = 20$; surgical operation/radiotherapy group, $n = 43$; healthy control group, $n = 44$). Women in the adjuvant tamoxifen group had received tamoxifen for a mean (SD) of 31.5 (18.6) months (range, 15–79 mo) and performed worse on verbal memory than the surgical operation/radiotherapy group ($P < 0.05$) and the healthy control group ($P < 0.05$). Participants in the adjuvant tamoxifen group performed worse on measures of fluency than healthy controls ($P < 0.05$). Furthermore, women in the adjuvant tamoxifen group reported worse cognitive functioning ($P < 0.05$) than women in the surgical operation/radiotherapy group or the healthy control group.

Conclusions: Our results provide insights into cognitive functioning in women who receive long-term adjuvant tamoxifen treatment. By adding the surgical operation/radiotherapy group, we could control for the mental and physical influences of the diagnosis and treatment of breast cancer. Cognitive domains that rely on verbal abilities (verbal memory and fluency) seem to be at risk for deterioration after treatment with tamoxifen.

Key Words: Tamoxifen – Cognition – Postmenopausal – Breast cancer.

With increased survival, cognitive functioning after breast cancer therapy becomes of greater importance to the well-being of women. In postmenopausal women, approximately 75% of breast tumors are hormone-sensitive.¹ In this group of women, endocrine therapy is widely used and often prescribed for many years.

Endocrine therapy aims to inhibit the growth of estrogen receptor (ER)-positive tumors by inhibiting or blocking estrogen. This can be achieved by administering either selective ER modulators (SERMs), which allow selective inhibition or stimulation of estrogen-like action in various tissues, or aromatase

inhibitors (AIs), which block the synthesis of estrogen, thus lowering estrogen levels. These endocrine therapies may be provided in a switch schedule (initially SERMs for a number of years followed by an AI up to a total of 5–7 y of endocrine therapy).^{2,3} Common adverse effects of endocrine therapy, such as hot flashes and mood disturbances, are related to estrogen deprivation.⁴ Increasing evidence suggests that estrogens play a role in cognitive functioning.⁵ Although the mechanisms of action of estrogens on the brain are not entirely understood, neuroscientific studies indicate that estrogens exert neurotrophic and neuroprotective actions.⁶ Estrogens seem to favor differentiation and survival by acting through ERs,⁷ but estrogens also act through membrane receptors to influence the functioning of the brain.⁸ These ERs are present in structures that are important for cognitive functioning, such as the frontal lobe and the hippocampus.⁹ Therefore, it is biologically plausible that endocrine therapy could affect cognitive functioning. Moreover, because estrogen is known to interact with the cholinergic system,¹⁰ it seems probable that cognitive functions such as attention, verbal learning, and memory may be particularly vulnerable.

Although much is already known about the cognitive effects of chemotherapy,¹¹ many women with breast cancer receive

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