CORRESPONDENCE

Re: The Effects of Tamoxifen and Estrogen on Brain Metabolism in Elderly Women

Tamoxifen is a selective estrogen receptor modulator (SERM) with mixed agonist/antagonist properties and variable, though consistent, effects upon target tissues. Although tamoxifen confers beneficial properties of an estrogen agonist on bone and on the cardiovascular system, it remains unclear how tamoxifen might influence the central nervous system or cognitive ability. The occurrence of hot flashes, a common side effect of tamoxifen treatment, in approximately 40% of patients implies that this agent exerts effects on the brain; hot flashes are relieved by serotonin uptake inhibitors and are considered to be centrally mediated via brain stem pathways. These phenomena of hot flashes suggest that tamoxifen acts as an estrogen antagonist within the central nervous system, which, in the longer term, could lead to a cognitive deficit.

There are limited clinical data indicating that breast cancer treatments that involve combinations of tamoxifen and chemotherapy are associated with impairment of cognitive function (1). Confounding factors make it difficult to determine the precise effects of tamoxifen when chemo-hormonal therapies are administered in combination. The study by Ernst et al. (2) provides reassuring evidence that tamoxifen may act as an estrogen agonist in the context of cerebral targets and that it may offer some degree of protection from the cognitive attrition that is associated with aging. Estrogens are thought to have a positive influence on brain metabolism and cognitive function, which is consistent with a 29% reduction in the incidence of Alzheimer’s disease among users of hormone replacement therapy compared with non-users (3). Moreover, as cited by Ernst et al. (2), there is evidence for reduced incidence of Alzheimer’s disease among women previously treated with tamoxifen (4). Longer-term follow-up studies with more rigorous psychometric assessment of patients on tamoxifen treatment are required to confirm any sparing of cognitive loss. Such studies are more likely to be forthcoming and to encompass a broader age range as patients undergo primary treatment for earlier-stage breast cancer and experience more prolonged survival. Nonetheless, there are concerns about whether impairment of cognitive function is associated with treatments that induce states of estrogen deprivation. This issue has been highlighted with the recent publication of findings from the Arimidex, Tamoxifen Alone, or in Combination (ATAC) trial that investigated the use of selective aromatase inhibitors as first-line adjuvant treatment for early breast cancer (5,6). These agents may prove to have enhanced antitumor efficacy compared with tamoxifen (hazard ratio for time to recurrence = 0.83, 95.2% confidence interval = 0.71 to 0.96; P = .0129), but they may lack the beneficial estrogen agonist activity in tissues such as bone and, possibly, in the brain. These latter properties characterize SERMs that possess a triphenylbutenone core and basic side chain. The composition of this side chain and its interaction with surface amino acids within the SERM–estrogen receptor complex determines estrogenicity and confers a pleiotropic functional profile (7). The preliminary analysis of data from the ATAC trial led the authors to conclude that further evaluation of the effects of aromatase inhibitors on bone mineral density and cognitive function is mandatory in order to fully assess the clinical risk–benefit ratio for these agents compared with that for tamoxifen. Concerns over these two effects may hinder the imminent and widespread introduction of selective aromatase inhibitors as first-line adjuvant hormonal therapies for early breast cancer and may preclude their use as chemopreventive agents in otherwise healthy individuals for whom the overall risks may outweigh objective benefits.

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RESPONSE

Results from our recent report (1) demonstrate that tamoxifen may have a similar, possibly positive, effect on brain metabolism to that of estrogen. Benson (2) emphasizes that preliminary results from the Arimidex, Tamoxifen Alone, or in Combination (ATAC) trial make it mandatory to study the effects of Arimidex (anastrozole) on bone mineral density and cognitive function. According to Benson, the concerns about these preliminary results may delay the wide use of anastrozole for treatment of early breast cancer and may preclude its use as a chemopreventive treatment in healthy women.

The uncertainty regarding potential side effects of such drugs is exacerbated by the fact that little is known about the organ- or cell type-specific actions of drugs that interfere with estrogen metabolism. Benson suggests that the effects of anastrozole, an aromatase inhibitor, on cognition and bone density might differ from those of tamoxifen, a selective estrogen receptor modulator (SERM), because these two drugs differ in their core structures and basic side chains. Yet even drugs that belong to
same class, such as the two SERMs tamoxifen and raloxifene, differ in their estrogenic side effect profiles. For example, tamoxifen is associated with an increased risk of endometrial cancer, whereas raloxifene may not be. One possible mechanism underlying this differential action of tamoxifen versus raloxifene was recently reported by Shang and Brown (3), who demonstrated that the difference in endometrial cancer risk was associated with a high level of steroid receptor coactivator-1 (SRC-1) expression in the uterus, which caused estrogen-like activity by tamoxifen but not by raloxifene. However, it can be expected that other molecular mechanisms may cause additional differential drug side effects in the uterus and other organs. Currently, we can only speculate about the potential molecular effects of these drugs in the brain.

Therefore, we agree with Benson’s assessment that a careful evaluation of the side effect profile of anastrozole is necessary, and we propose that all agents that have the potential to influence estrogen function should be studied for their potential side effects on the brain and other organs. Some negative side effects of drugs used for successful treatment of breast cancer may well be acceptable. However, when these drugs are administered to a large number of healthy women for the purpose of preventing breast cancer, even seemingly rare side effects may easily outweigh the potential benefits provided by a reduction in breast cancer incidence.

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