Estrogens – the Saviors of Cognitive Function?

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In the past decades, major progress has been made regarding prognosis of patients with breast cancer. This is due to early detection programs and improvements in diagnosis on the one hand and a large variety of highly effective therapy options on the other hand. Chemotherapy is still the backbone of therapy in a prominent part of patients – especially the triple negative and HER2-positive ones. However, patients with hormone receptor-positive breast cancer are treated by targeted endocrine therapy and can often be spared chemotherapy. The advantage of targeted therapies is their high efficacy in combination with a good side effect profile.

Tamoxifen as well as aromatase inhibitors alone or in combination with GNRH (gonadotropin releasing hormone) agonists are generally well tolerated and much less toxic compared to chemotherapy, while they are at least as effective. Nonetheless, there are – somewhat in contrast to the data of clinical trials – bothersome side effects, which are sometimes the cause for incompliance or change of treatment. Hot flashes, arthralgia, weight gain, grade 1 alopecia, or diminished cognitive function as investigated by Berndt et al. [1] in this issue of BREAST CARE are reported by patients in daily clinical routine.

Even though these side effects are less severe compared to those of chemotherapy, we have to keep in mind two important things: i) Patients with hormone receptor-positive disease, especially postmenopausal ones, have a very good prognosis and a long life to life after diagnosis. After rehabilitation of breast cancer, they want to be and they are needed in their families – for instance to take care of grand children or to nurse their old mother or father. Additionally, retirement age is getting higher and they want to and/or have to go back to work. So even small disturbances, such as slightly impaired cognitive function might have a great impact to their life. ii) More and more data exist that long-term endocrine therapy consisting of 10–15 years of treatment lead to a better disease-free survival than 5 years only [2]. Therefore treatment related side effects will last for a long period of time.

In this issue Berndt et al. [1] investigate the impact of endocrine treatment on cognitive function, in detail on memory and spatial cognition. They focused on these domains as there is evidence that they are influenced by 17 β -estradiol.

Several studies suggest that estrogens have neuroprotective properties. Estrogens reduce apoptosis, have anti-inflammatory properties, and activate neurotrophic and regeneration associated genes. Even more, estrogens positively impact on cholinergic pathways in the brain including the hippocampus, which holds a central role for cognitive functioning, including memory [3]. Having this in mind, it seems more than reasonable for Berndt et al. to hypothesize that lowering estrogen serum levels to nearly zero by aromatase inhibitors will impair cognitive function.

Actually, there are conflicting data on cognitive function by tamoxifen, aromatase inhibitor, and estradiol, respectively. Estrogen replacement therapy after oophorectomy prevented impairment in verbal memory performance in one study and premature menopause led to higher risk of dementia in another study. In striking contrast, in women 65 years or older, estrogens increased the risk of dementia in another study (all summarized in [3]). So regarding cognitive function timing of the rise and fall of estrogen blood levels seems to be crucial.

Having in mind the agonistic and antagonistic properties of SERMs (selective estrogen receptor modulators), it seems reasonable that tamoxifen may have positive as well as negative influence on brain function, which indeed have been reported in various trials. Even more, expression of not only estrogen receptor (ER) but also ER β and possibly its splicing variants as well as expression of steroid receptor coactivator (SRC)-1 and -2 might modulate the effect of tamoxifen and estrogen deprivation by aromatase inhibitors on cognitive function [4]. Indeed, a sub-study of the chemoprevention trial IBIS II as well as a sub-study of the TEAM trial indicated that there is no impact of estrogen deprivation by aromatase inhibitors on cognitive function [5, 6].

So how do the results of Berndt and colleagues add to this? In a cross-sectional study on postmenopausal patients with breast cancer, who had no chemotherapy, they compare memory and spatial cognition in patients treated with aromatase inhibitors, tamoxifen, the SWITCH therapy, or local therapy only. They demonstrate a negative impact of estrogen deprivation by aromatase inhibitors on general memory in patients with aromatase inhibitors only, but not in patients with SWITCH therapy or tamoxifen. They also report

on the relationship between psychological changes and self-perception of cognitive function. Clearly, depression and anxiety, which can be a result of cancer diagnosis but also of ongoing cancer treatment, such as endocrine treatment, negatively impact on cognitive function. And even though they showed that there is no correlation between low self-perception of cognitive function and objective test results, an impact on daily living cannot be ruled out.

In any case, the impact on cognitive function will not be the major determinant for the decision of using aromatase inhibitors, tamoxifen, or SWITCH therapy now or in the future. However, the

present report alerts us to consider changes on cognitive function by endocrine therapy in the follow-up visits of our patients which even might be a reason to switch from one regimen to another – as we have to respect their body, their mind, and their soul.

Disclosure Statement

The author has nothing to disclose.

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