Ocular Surface Disease in Breast Cancer Patients Using Aromatase Inhibitors

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Abstract: Aromatase inhibitors (AIs) are widely used as adjuvant hormonal therapy in postmenopausal women with hormone receptor-positive breast cancer. The purpose of this study was to investigate the potential impact of AIs on the anterior segment of the eye and especially the ocular surface. Participants in our study were 41 hormone receptor-positive early stage breast cancer patients (80 eyes), treated with AIs, while 80 eyes of 40 age- and gender-matched healthy controls, not previously used AIs for any purpose, were also evaluated. All participants underwent a complete ophthalmological examination, including best corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, and dilated fundus examination. Ocular surface disease-related symptoms and signs were also recorded. The most common symptom was found to be blurred vision, while other symptoms included foreign body sensation, tearing, redness, and photophobia. Slit-lamp examination revealed blepharitis and meibomian gland dysfunction in 75% and 42.5% of patients, respectively. Superficial punctate keratitis and conjunctival injection were also present. Our results demonstrated a high prevalence of ocular surface disease-related symptoms and signs in patients receiving AIs compared to healthy controls. This study may raise a flag regarding the use of AIs. However, further and larger prospective longitudinal studies are needed to examine the possible effect of AIs alone or in combination with chemotherapy in the eyes of breast cancer patients.

Key Words: aromatase, breast, ocular surface

Aromatase inhibitors (AIs), such as anastrozole, letrozole, and exemestane, are widely used as adjuvant hormonal therapy in post-menopausal women with hormone receptor-positive breast cancer. These nonsteroidal inhibitors interfere with aromatase, the enzyme that converts androgen from the adrenals and peripheral tissues to estrogens. Specifically, anastrozole and letrozole are competitive inhibitors, whereas exemestane permanently binds to and irreversibly inactivates aromatase. None of these agents inhibit adrenal corticosteroid or aldosterone biosynthesis (1).

The effects of estrogen are mediated through alpha and beta estrogen receptors, which are both expressed in the human retina (2). Ocular side effects of AIs, including visual disturbances, retinal hemorrhages, hemiretinal artery occlusion, vitreoretinal traction, corneal epithelial cysts, and dry eye, have been previously reported (3–6). Recently Moschos et al. demonstrated a significant difference in visual acuity, retinal nerve fiber layer thickness and visual evoked potentials findings between patients receiving AIs and healthy controls, suggesting that AIs have an impact on the retina and optic nerve function (7). These findings could be attributed to the inhibition of estrogens’ biosynthesis by AIs, which may deprive the retina and the choroid from the beneficial and protective effects mediated by estrogens (8).

Recently Inglis et al. have found that AI users have a higher prevalence of dry eye syndrome compared to controls, suggesting that routine screening with the ocular surface disease index would be useful for such patients, so as to improve quality of life (9). In light of the above, the purpose of this study was to investigate the potential impact of AIs on the anterior segment of the eye and especially the ocular surface.
METHODS

The study sample was derived from a pool of patients \((n = 70)\) after the application of exclusion criteria. Specifically, 15 patients were excluded due to nonophthalmological reasons (nine had hypertension and six had diabetes mellitus) and eight patients due to ophthalmological reasons (five had age-related macular degeneration and three had glaucoma). Six patients had used tamoxifen previously and were also excluded. Therefore, 41 patients were eligible for the study. Two of the 82 eyes (41 patients) were not included in the analysis due to cataract and amblyopia, so as to exclude any ocular pathology. As a result, participants in our study were 41 hormone receptor-positive early stage breast cancer patients (80 eyes), treated with AIs. Previous administration of adjuvant chemotherapy (anthracycline and taxane based) was permitted 4 months prior to the enrollment to the study; however, patients who had received tamoxifen, zoledronic acid, and/or trastuzumab were excluded from the final analysis. In our study, seven patients (17.5%) have received previous chemotherapy.

All participants did not have any ocular or systemic disorder other than breast cancer, so as to reduce confounding factors that could complicate our data and results, while 80 eyes of 40 age- and gender-matched healthy controls, not previously used AIs for any purpose, were also evaluated. The protocol of the study was approved by the institutional review board of our hospital and was in accordance with the tenets of the Declaration of Helsinki. All participants underwent a complete ophthalmological examination, including best corrected visual acuity (BCVA) assessment, slit-lamp biomicroscopy, and dilated fundus examination. Ocular surface disease-related symptoms and signs were also recorded.

RESULTS

Table 1 shows the demographic and clinical characteristics of our study sample. The mean age of patients was \(62.0 \pm 9.2\) years. The BCVA was \(0.9 \pm 0.15\) (decimal scale). 37.5% of the examined eyes received letrozole, 33.8% anastrozole and 28.7% exemestane. The duration of AI use was \(2.6 \pm 1.1\) years.

The symptoms and ocular signs related to the anterior segment of the eye are shown on Table 2. The most common symptom was found to be blurred vision (47.5%), while other symptoms included foreign body sensation (30%), tearing (22.5%), redness (15%), and photophobia (2.5%). All symptoms were of mild to moderate severity, even they seemed to be disturbing for patients. The mean time from initiation of the AIs to the first reported symptom was \(13.2 \pm 12.6\) months. Slit-lamp examination revealed blepharitis and meibomian gland dysfunction (MGD) in 75% and 42.5% of patients, respectively. Superficial punctate keratitis and conjunctival injection were also present in 30% and 22.5%, respectively. All reported parameters, except photophobia, differed significantly \((p < 0.001\) for all parameters) between AI users and controls.

DISCUSSION

Our results demonstrated a high prevalence of ocular surface disease-related symptoms and signs in patients receiving AIs compared to healthy controls, in

| Table 1. Demographic and Clinical Characteristic in Our Study Sample |
|--------------------------|--------------------------|
| **Aromatase Inhibitors users \((n = 80)\)** | **Controls \((n = 80)\)** |
| **Demographic and clinical characteristics** | |
| Age (years), mean ± SD | 62.0 ± 9.2 | 61.5 ± 8.7 |
| Best corrected visual acuity (decimal), mean ± SD | 0.9 ± 0.15 | 1.0 ± 0.0 |
| Duration of aromatase inhibitors use (years), mean ± SD | 2.6 ± 1.1 | N/A |
| **Aromatase inhibitors** | |
| Letrozole, \(N\) (%) | 30 (37.5) | N/A |
| Anastrozole, \(N\) (%) | 27 (33.8) | |
| Exemestane, \(N\) (%) | 23 (28.7) | |

| Table 2. Self-Reported Symptoms and Ocular Signs Related to the Anterior Segment of the Eye in Aromatase Inhibitors’ Users |
|--------------------------|--------------------------|
| **Aromatase Inhibitors users \((n = 80)\)** | **Controls \((n = 80)\)** |
| Self-reported symptoms | |
| Blurred vision | 19 (47.5) | 3 (7.5) |
| Foreign body sensation | 12 (30) | 6 (15) |
| Tearing | 9 (22.5) | 3 (7.5) |
| Redness | 6 (15) | 2 (5) |
| Photophobia | 1 (2.5) | 1 (2.5) |
| Ocular signs in slit-lamp biomicroscopy | |
| Blepharitis | 30 (75) | 10 (25) |
| Meibomian gland dysfunction | 17 (42.5) | 5 (12.5) |
| Superficial punctate keratitis | 12 (30) | 3 (7.5) |
| Conjunctival injection | 9 (22.5) | 2 (5) |
line with Turaka et al. and Inglis et al., who reported dry eye syndrome in AI users (6,9). Specifically, patients receiving AIs in our study presented blepharitis in 75%, while MGD was found to be less common (42.5%), but associated with dry eye symptoms.

Meibomian gland dysfunction, a major form of blepharitis, is a common chronic disease of the posterior eyelids, whose exact pathogenetic mechanism remains unknown. Potential causes of MGD could be the altered composition of the meibum or the obstruction of the meibomian glands, leading to altered tear film lipid layer, increased evaporation of the tears and dry eye symptoms, such as foreign body sensation, tearing, and blurred vision (10). Hormone triggering has been also implicated in the pathophysiology of MGD; therefore, our observation that patients receiving AIs present MGD in a higher percentage than controls may be attributed to the AI-induced deprivation of estrogens, as sex hormones play an important role in the maintenance of normal tear film as well (6).

A potential limitation of our study pertains to the fact that it was a cross-sectional study. The optimal design includes a longitudinal study with baseline data, investigating the possible effect of AIs on the eyes during time. As a result, one cannot conclude whether the observed changes are stable, progressive, or regressive following discontinuation of the drug.

In conclusion, this study may raise a flag regarding the use of AIs, informing patients and clinicians of the association between the use of AIs and ocular surface disease symptoms. However, further and larger prospective longitudinal studies are needed to examine the possible effect of AIs alone or in combination with chemotherapy in the eyes of breast cancer patients.

**CONFLICT OF INTEREST**

None.

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