Choroidal thickness, ganglion cell complex and photoreceptor outer segment length evaluation in patients receiving tamoxifen therapy by spectral domain optical coherence tomography

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Research article

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Abstract

Background To evaluate choroidal thickness, ganglion cell complex and photoreceptor outer segment length in patients with breast cancer undergoing tamoxifen therapy using spectral domain optical coherence tomography (SD-OCT) and to compare the results to normal eyes. **Methods** Forty four patients with breast cancer undergoing tamoxifen therapy and forty one healthy controls were included in this prospective, comparative study. All participants underwent a complete ophthalmologic evaluation and SD-OCT. Subfoveal, nasal (nasal distance to fovea 500 μ m, 1000 μ m, 1500 μ m) and temporal (temporal distance to fovea 500 μ m, 1000 μ m, 1500 μ m) choroidal thickness measurements were performed using enhanced depth imaging mode of SD-OCT. Using an Early Treatment Diagnostic Retinopathy Study (ETDRS) circle at the macular level, the automated retinal segmentation software was applied to determine thicknesses of the ganglion cell complex (GCC) by adding the macular retinal nerve fiber layer, macular ganglion cell layer, and macular internal plexiform layer parameters. The photoreceptor outer segment (PROS) length was determined by manually as the distance from inner surface of ellipsoid zone to inner surface of retina pigment epithelium after automatic retinal segmentation. **Results** The mean choroidal thickness measurements were statistically greater in tamoxifen group than controls in all quadrants ($p < 0.001$ for all quadrants). Of all tamoxifen users (44 eyes of 44 patients), 33 eyes (75%) had uncomplicated pachychoroid (UCP). Pachychoroid pigment epitheliopathy (PPE) was detected in 5 patients (11.3%) in tamoxifen group. Patients with PPE in one eye had UCP in the fellow eye. Central serous chorioretinopathy findings were observed in one patient. Tamoxifen users had statistically lower GCC thicknesses in all inner rings of ETDRS inlay and only in nasal outer ring ($p: 0.027$, $p: 0.002$, $p: 0.002$, $p: 0.001$ and $p: 0.030$; respectively). No statistically significant difference was found between the groups in terms of mean subfoveal PROS length. **Conclusions** SD-OCT provides valuable information in identifying the structural changes and evaluation of ocular findings in patients receiving tamoxifen therapy. Increasing choroidal thickness, PPE, thinning GCC were detected in tamoxifen users. These OCT findings may be an early indicator of retinal toxicity for patients undergoing tamoxifen therapy in follow-up period.

Background

Tamoxifen, a selective estrogen receptor modulator, is recommended to treat early and advanced-stage breast cancer in premenopausal and postmenopausal women [1]. It reduces the available estrogen to cancer cells by competitively inhibiting the binding of estrogen to the estrogen receptors on breast tissues [2].

Tamoxifen has been used for many years and the side effects are well documented. Common side effects of tamoxifen are thromboembolic events, gynecological symptoms, major depression, and musculoskeletal symptoms [3]. The ocular side effects of tamoxifen such as cataract [4], keratopathy [5], optic neuritis [6] has been previously reported. Also crystalline maculopathy [7], macular hole [8],

pseudocystic foveolar cavitation [9], pachychoroid pigment epitheliopathy [10], branch retinal vein occlusion [11] have been reported as tamoxifen associated retinal pathologies. We aimed to evaluate structural changes by spectral domain optical coherence tomography (SD-OCT) before development of pathological retinal findings.

Methods

This prospective, comparative clinical study was carried out between September 2018 and January 2019 in Okmeydani Training and Research Hospital, Istanbul, Turkey. Informed consent was obtained from all participants and the study was carried out in agreement with the Declaration of Helsinki for research involving human subjects. There were two groups consisting of patients with breast cancer undergoing tamoxifen therapy who were being followed at Okmeydani Training and Research Hospital Radiation oncology clinic while the control group was formed by age and gender matched healthy subjects who were examined at the Eye Clinic of the same hospital. Patients who have received tamoxifen therapy for less than one year were not included in the study. All the patients were receiving tamoxifen 20 mg per a day.

Retinal diseases (such as epiretinal membrane, vein occlusion, macular hole, vitreomacular traction syndrome, diabetic retinopathy), any systemic disorders, previous ocular surgery and trauma, congenital malformations of the eye, glaucoma and ocular hypertension, significant media opacities precluding fundus examination and/or imaging, best corrected visual acuity (BCVA) worse than 20/20, spherical equivalent refractive errors of more than ± 3 dioptre, any medications within the last three months, history of smoking or alcohol intake and pregnancy were evaluated as an exclusion criteria. All the participants hemoglobin, blood vitamin D, vitamin B12, iron, thyroid functional tests (T3, T4, TSH) levels and systolic and diastolic blood pressures values were within the normal range.

A complete ophthalmic examination, including the measurement of the BCVA using Snellen charts, Goldmann applanation tonometry, slit-lamp biomicroscopy and dilated fundus examination was conducted. Axial length (AL) was evaluated with AL-Scan optical biometer (Nidek Co., Gamagori, Japan). Choroidal thickness was measured using Enhance depth imaging (EDI) mode of an SD-OCT (Spectralis HRA+OCT; Heidelberg Engineering Inc, Heidelberg, Germany). Twenty-five, each comprised of 40 averaged scans, were obtained in $10^{\circ} \times 20^{\circ}$ rectangle centered on the fovea. The choroid was measured from the outer portion of the hyperreflective line corresponding to the retinal pigment epithelium-Bruch's membrane complex to the inner surface of the sclera/choroidal junction (manually

drawn by examiner). All SD-OCT measurements were performed between 10:00 and 11:00 am. Subfoveal, nasal and temporal measurements of the choroidal thickness was conducted manually. Nasal and

temporal choroidal thickness measurements were carried out 500 µm intervals from the fovea centralis (500, 1000 and 1500 µm distance to the fovea centralis) (Figure 1).

Choroidal thicknesses of eyes with pachychoroid phenotype are greater than 300 µm together with and without retina pigment epithelium abnormalities were evaluated as uncomplicated pachychoroid (UCP) and pachychoroid pigment epitheliopathy (PPE) respectively [12].

Using an Early Treatment Diagnostic Retinopathy Study (ETDRS) circle at the macular level, the automated retinal segmentation software was applied to determine thicknesses of the ganglion cell complex (GCC) by adding the macular retinal nerve fiber layer, macular ganglion cell layer, and macular internal plexiform layer parameters (Figure 2).

The photoreceptor outer segment (PROS) length was determined by manually as the distance from ellipsoid zone to inner surface of retina pigment epithelium (RPE) after automatic retinal segmentation (Figure1).

Only the right eye of each participants was evaluated for statistical analysis. Choroidal thickness, PROS length were measured manually by two independent graders without knowledge of information of the subjects and the average measurements were used in statistical analysis.

Statistical analyses were performed using the IBM SPSS Statistics version 21. The variables were investigated using histograms and analytical methods to find out whether or not they are normally distributed. The Student's t-test was used to compare the variables between the groups. The effects of age and axial length was adjusted using ANCOVA tests. A 5% type-1 error level was used to infer statistical significance.

Results

A total of 85 eyes were enrolled into this prospective, case-control study. Forty-four patients constituted tamoxifen group, whereas forty-one age and sex matched subjects constituted control group. All of the participants were female. The mean age was 51.6 ± 7.4 years in tamoxifen group and 52.0 ± 5.5 years in controls ($p: 0.786$). The mean duration of tamoxifen use in the study group was 3.95 ± 1.91 (1-9) years. The groups were comparable regarding to axial lengths (22.7 ± 0.4 vs 22.7 ± 0.3 ; $p: 0.713$).

The mean choroidal thickness measurements were statistically greater in tamoxifen group than controls in all quadrants ($p < 0.001$ for all quadrants). The results are shown in Table 1. Figure 3 shows that the choroidal thickness was significantly thicker at all predefined measurement points in tamoxifen group (all $p < 0.001$). Of all tamoxifen users (44 eyes of 44 patients), 33 eyes (75%) had UCP. PPE was detected in 5 patients (11.3%) in tamoxifen group. Patients with PPE in one eye had UCP in the fellow eye. Central serous chorioretinopathy (CSCR) findings were observed in one patient. The SD-OCT and infrared reflectance (IR) images of patients with PPE and CSCR were presented in Figures 4 and Figure 5 respectively.

Tamoxifen users had statistically lower GCC thickness in all inner rings of ETDRS inlay and only in nasal outer ring ($p:0.027$, $p:0.002$, $p:0.002$, $p:0.001$ and $p:0.030$; respectively) (Table-2).

No statistically significant difference was found between the groups in terms of mean subfoveal PROS length, mean central macular thickness (CMT) and GCC thickness in the rest of outer rings ($p:0.640$, $p:0.144$, $p:0.122$, $p:0.233$ and $p:0.468$; respectively) (Table-2 and Table-3).

Discussion

Tamoxifen associated ocular toxicity is estimated to be between 0.9% and 12% [13]. Generally ocular toxicity occurs with high dose therapy (cumulative dose > 100 g) [14]. There are no controlled studies evaluating structural optical coherence tomography (OCT) changes regarding tamoxifen therapy in literature. Reported OCT findings associated with tamoxifen depends on case series and these findings are ellipsoid zone defect, thinning of the inner retinal layers, cystic foveal cavitation, crystalline deposits in the inner retina [15].

In our study the mean choroidal thickness measurements at subfoveal, nasal and temporal quadrants were all greater in tamoxifen users than control group. 75% of all tamoxifen users had UCP. PPE was detected in 5 patients (11.3%). Pachychoroid spectrum diseases are UCP, PPE, CSCR, pachychoroid neovascularopathy, and polypoidal choroidal vasculopathy. Characteristics of PPE are increased choroidal thickening, pathologically dilated veins in the Haller's layer, thinning in Sattler's and choriocapillaris layers, variety of retina pigment epithelium abnormalities at the macula with lack of subretinal fluid and drusen. There is only one case report indicating PPE associated with tamoxifen [10]. There are studies showing different combinations of this spectrum in the same patient [16]. In our study, 5 patients with PPE in one eye had UCP in the fellow eye. We indicated CSCR findings in a patient receiving tamoxifen therapy. The risk factors for CSCR are well documented and these are exogenous cortisol therapies, endogenous hypercortisolism, male sex, exogenous testosterone therapy, polycystic ovary syndrome [17,18,19]. Also it has shown in several studies that choroidal thickness increases in various inflammatory diseases such as Vogt-Kayanagi Harada disease, FMF disease [20,21].

Estrogen receptors (ER) in the retina firstly demonstrated in the rats [22] and then both types of ER receptors (ER α and ER β) [23] were identified in human retinas. Tamoxifen is a partial agonist, which activates the estrogen receptor-alpha (ER α) with lower efficacy compared to estrogen [24]. Reduced

expression of ER α have been shown to be associated with CSCR [25]. In addition to this, serum testosterone, cortisol and cortisone levels increase during tamoxifen therapy [26]. Testosterone have been shown to increase choroidal vascular permeability and vascular dilatation [27]. These mechanisms may explain increasing choroidal thickness, development of PPE and CSCR in tamoxifen users.

It has shown that tamoxifen is toxic to human RPE and photoreceptors in vitro studies [28]. Maculopathy associated with tamoxifen have been demonstrated previous reports. There are case series in literature including crystalline maculopathy [7], macular hole [8], pseudocystic foveolar cavitation [9]. However there are no previous report evaluating macula, GCC thicknesses and PROS length.

This study may be important in terms of demonstrating the relationship between the use of tamoxifen and GCC thickness reduction. Tamoxifen associated optic neuropathy has been previously reported [6]. Retinal ganglion cell (RGC) layer thinning occurs earlier than retinal nerve fiber layer (RNFL) thinning after acute optic neuropathies and quantification of the macular RGC layer thickness may provide more valuable information for neuronal damage than RNFL thickness [29]. Toxic optic neuropathies are primarily due to injury of the RGC layer [30]. This suggest that ganglion cell toxicity has an important role in the development of toxic optic neuropathy. In our study we indicated that tamoxifen users had lower GCC thicknesses in all inner ring and nasal outer ring of ETDRS inlay. In addition to ganglion cell toxicity reduction in GCC thickness in tamoxifen users could be related to vascular changes at choroidal level. Demirok et al. demonstrated that GCC is significantly reduced in both acute and chronic CSCR subjects compared with healthy subjects [31]. Increasing choroidal thickness measurements, development of PPE and CSCR, reducing GCC thickness measurements in the tamoxifen group support this report.

There are four hyperreflective outer retinal lines that directly effects the visual prognosis on SD-OCT. These are from inner to outer retina: external limiting membrane, ellipsoid zone, cone outer segment tips and RPE. Photoreceptors have two apical compartments: the inner segments and the outer segments. The PROS is located in between ellipsoid zone and RPE.

Under the fovea centralis are Müller cells and cone photoreceptors packed at their highest density, an area known as the central bouquet of cones [32]. This region is a very special area in terms of visual function and disruption of architecture in this area effects visual function directly. There are some reports regarding the effect of PROS length on visual prognosis. Shiono et al. showed PROS length as a good indicator of best corrected visual acuity in postoperative period of epiretinal membrane surgery [33]. Uslu et al. detected the PROS length thinning in patients with hydroxychloroquine therapy [34]. We pointed out that tamoxifen did not effect subfoveal PROS length.

Conclusions

There is no established monitoring method in order to follow-up ocular side effects of tamoxifen already. SD-OCT may provide valuable information for understanding retinal structural changes in patients undergoing tamoxifen therapy. Even if no pathological retinal findings were found in the fundoscopic examination, structural changes may be began in the SD-OCT examination. Thickening of choroid and thinning of GCC may be an early indicator of retinal toxicity for tamoxifen users in follow-up period.

Abbreviations

SD-OCT: spectral domain optical coherence tomography; AL: axial length; EDI: enhanced depth imaging; UCP: uncomplicated pachychoroid; PPE: pachychoroid pigment epitheliopathy; ETDRS: early treatment diagnostic retinopathy study; GCC: ganglion cell complex; PROS: photoreceptor outer segment; RPE: retina pigment epithelium; CSCR: central serous chorioretinopathy; IR: infrared reflectance; CMT: central macular thickness; OCT: optical coherence tomography; ER: estrogen receptor; RGC: retinal ganglion cell; RNFL: retinal nerve fiber layer

Declarations

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Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' contributions

SB conceived the idea. SB and OKG participated in the design of the study. OKG and GK collected the data. AC and BE performed the statistical analysis. SB, OKG, AC, BE and GK drafted the manuscript and performed the manuscript reviews. All authors were involved in manuscript preparation and further revisions. All authors read and approved the final manuscript for publication and agreed to be personally accountable for their contributions.

Ethics approval and consent to participate

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Ethics committee approval for ophthalmological examination and using the results of research and data analysis in breast cancer patients undergoing tamoxifen therapy was obtained from the Marmara University Medical Faculty Ethic Committee, Turkey (approval number 09.2018.427). The research adhered to the tenets of the Declaration of Helsinki. The written informed consent to participate in the study and section of the manuscript was obtained from all individuals enrolled for the study.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Mean choroidal thickness measurements of tamoxifen and control groups

Choroidal thickness	Tamoxifen group (n:44)	Control group (n:41)	P value
Subfoveal (mean±SD, mm)	367.9±74.2	277.9±45.0	<0.001
(min-max)	240-528	180-388	
Temporal 500 (mean±SD, mm)	361.4±72.2	267.9±48.8	<0.001
(min-max)	245-515	180-379	
Temporal 1000 (mean±SD, mm)	345.0±71.3	262.7±49.2	<0.001
(min-max)	217-515	182-370	
Temporal 1500 (mean±SD, mm)	325.2±72.2	248.4±51.5	<0.001
(min-max)	209-496	149-354	
Nasal 500 (mean±SD, mm)	350.5±74.6	259.6±45.1	<0.001
(min-max)	235-514	168-363	
Nasal 1000 (mean±SD, mm)	331.2±73.0	247.9±44.9	<0.001
(min-max)	216-510	154-357	
Nasal 1500 (mean±SD, mm)	309.2±70.6	233.3±49.8	<0.001
(min-max)	181-482	138-333	

Table2. Mean ganglion cell complex thickness measurements in tamoxifen and control groups

Ganglion cell complex thickness	Tamoxifen group (n:44)	Control group (n:41)	P value
Superior inner ring (mean±SD, mm)	115.2±14.2	120.9±8.2	0.027
(min-max)	76-161	100-137	
Inferior inner ring (mean±SD, mm)	110.9±14.2	118.9±8.2	0.002
(min-max)	69-146	102-139	
Nasal inner ring (mean±SD, mm)	107.2±12.8	115.2±9.4	0.002
(min-max)	73-132	90-140	
Temporal inner ring (mean±SD, mm)	97.0±11.1	104.5±8.0	0.001
(min-max)	64-122	92-126	
Superior outer ring (mean±SD, mm)	101.3±9.6	104.4±8.3	0.122
(min-max)	78-128	87-122	
Inferior outer ring (mean±SD, mm)	103.0±9.4	105.3±8.3	0.233
(min-max)	76-127	88-122	
Nasal outer ring (mean±SD, mm)	115.7±11.6	120.6±8.8	0.030
(min-max)	75-141	101-144	
Temporal outer ring (mean±SD, mm)	89.2±7.9	90.3±6.1	0.468
(min-max)	73-113	75-104	

Table 3. Mean Photoreceptor Outer Segment (PROS) lenght and central macular thickness (CMT) measurements in tamoxifen and control groups

	Tamoxifen group (n:44)	Control group (n:41)	P value
Subfoveal PROS (mean±SD, mm)	58.6±4.2	59.0±3.8	0.640
(min-max)	47-68	51-69	
CMT (mean±SD, mm)	253.6±17.1	259.4±18.7	0.144
(min-max)	218-304	225-299	

Figures

Figure 1

A representative enhanced depth imaging (EDI) mode of spectral domain optical coherence tomography (SD-OCT) image showing the choroidal thickness and photoreceptor outer segment length measurements of a breast cancer patient receiving tamoxifen therapy.

Figure 2

Retinal thickness analysis using an Early Treatment Diagnostic Retinopathy Study (ETDRS) circle at the macular level after automated retinal segmentation software was applied. In the image, the ganglion cell layer measurements of a breast cancer patient receiving tamoxifen therapy are shown as an example.

Figure 3

Comparison of choroidal thickness measurements at predefined measurements points in tamoxifen and control group. P values above the boxes show statistical significance when comparing the choroidal thickness measurements of two groups.

Figure 4

An infrared reflectance image (A) and enhanced depth imaging (EDI) mode of spectral domain optical coherence tomography (SD-OCT) image (B) of a 46-year-old female patient with breast cancer. She has been using tamoxifen for 5 years. Irregular hyperreflectivity appears on the infrared reflectance image of the lesion. In the SD-OCT image, pachyveins (enlargement of Haller's layer) under the retinal pigment epithelium (RPE) change and thick choroid (choroidal thickness under RPE change: 361 μm) is seen. Subfoveal choroidal thickness is 414 μm.

Figure 5

An infrared reflectance image (A) and enhanced depth imaging (EDI) mode of spectral domain optical coherence tomography (SD-OCT) image (B) of a 56-year-old female patient with breast cancer. She has

been using tamoxifen for 7 years. A small central serous chorioretinopathy (CSCR) area is seen at nasal side of the fovea. In the SD-OCT image, large pachyveins (enlargement of Haller's layer) under the subretinal fluid and thick choroid (choroidal thickness under CSCR: 323 μ m) is seen. Subfoveal choroidal thickness is 349 μ m.